BJA

British Journal of Anaesthesia

International Journal of Anaesthesia

Volume 84 Number 5 May 2000

Editor-in-chief: Jennifer M. Hunter

- Is hyperbaric oxygen therapy of use in CO poisoning?
- Do potent inhalational agents affect NO estimation?
- Oesophageal perforation and TOE

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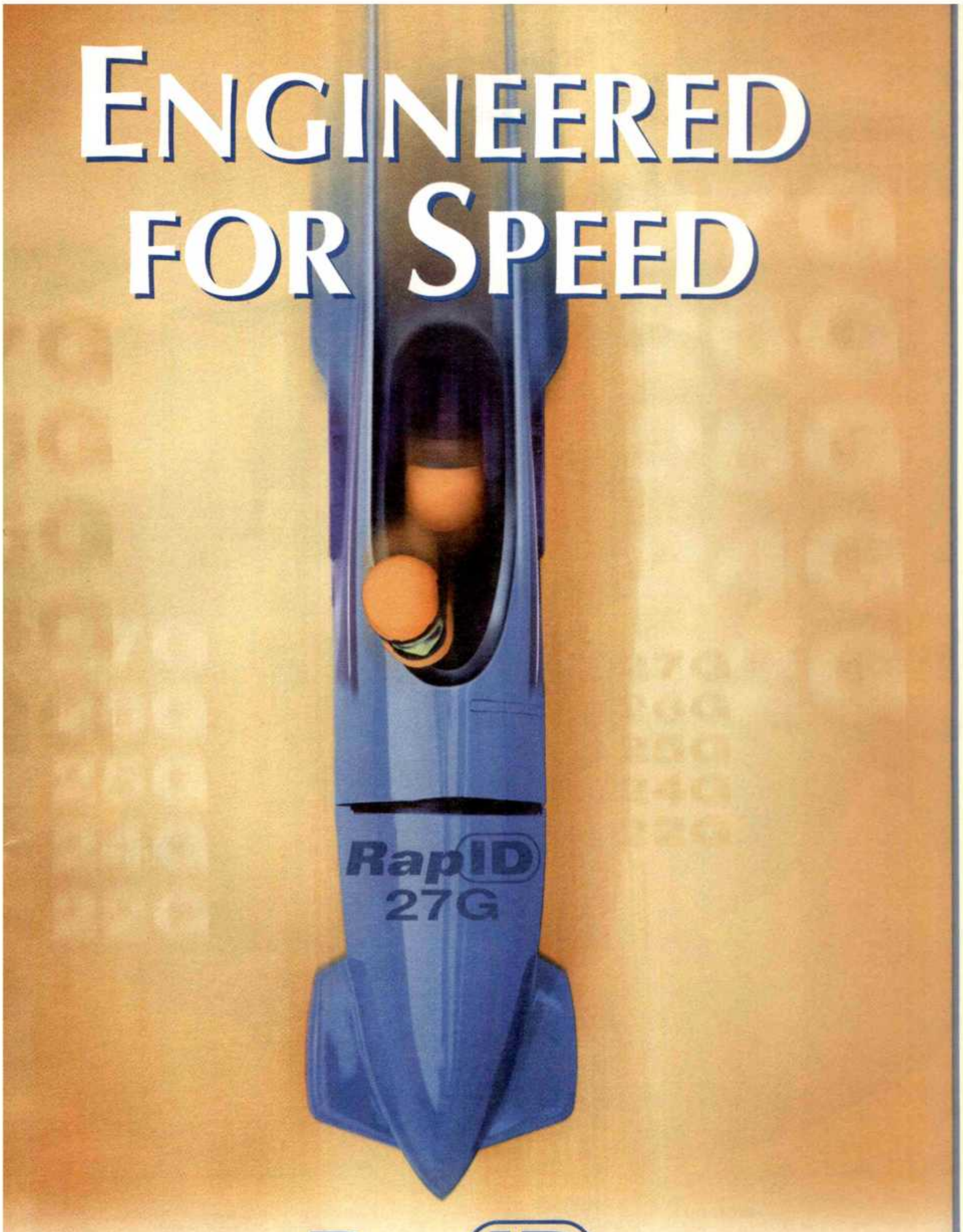

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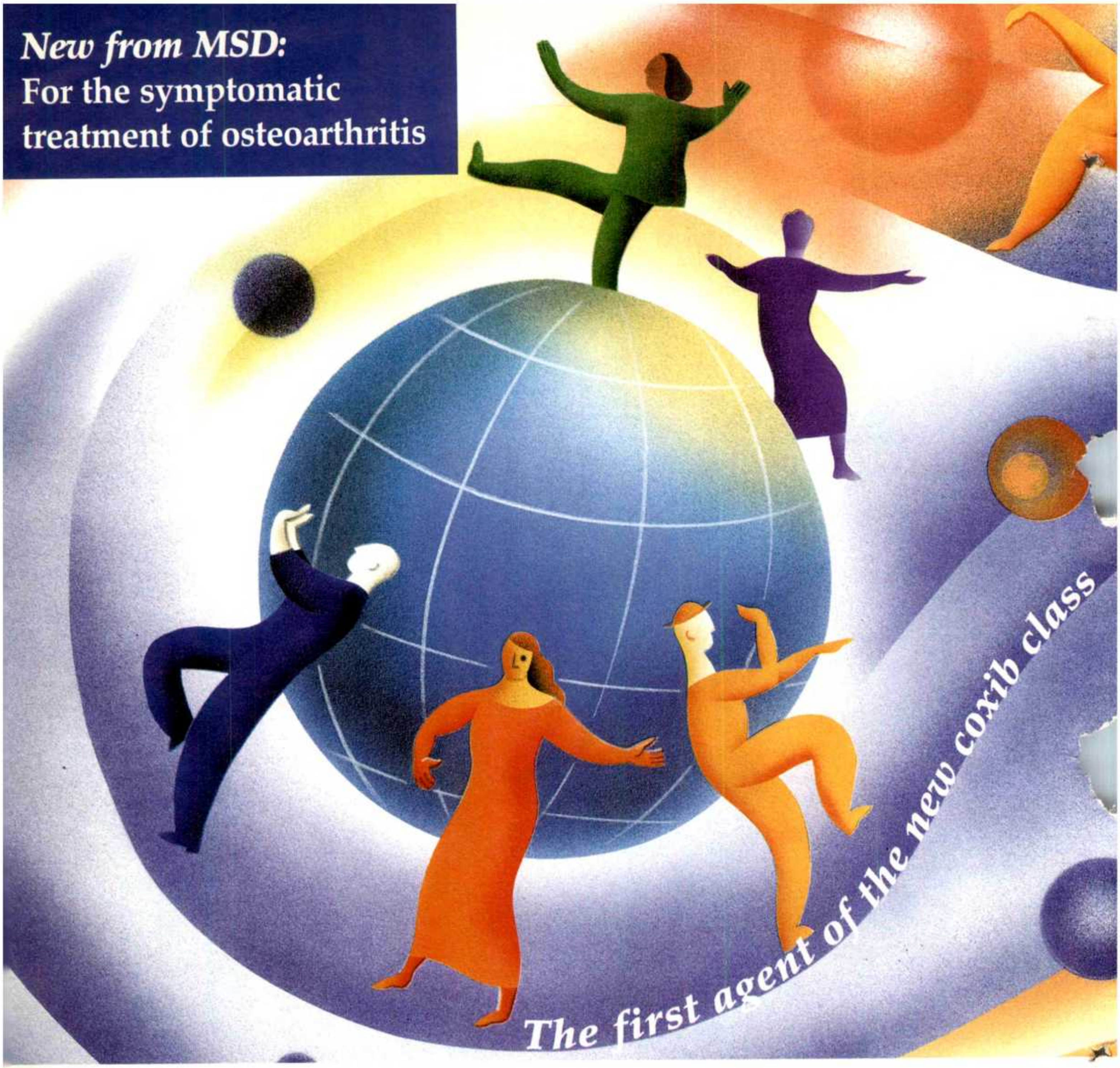
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PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib.

Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension.

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

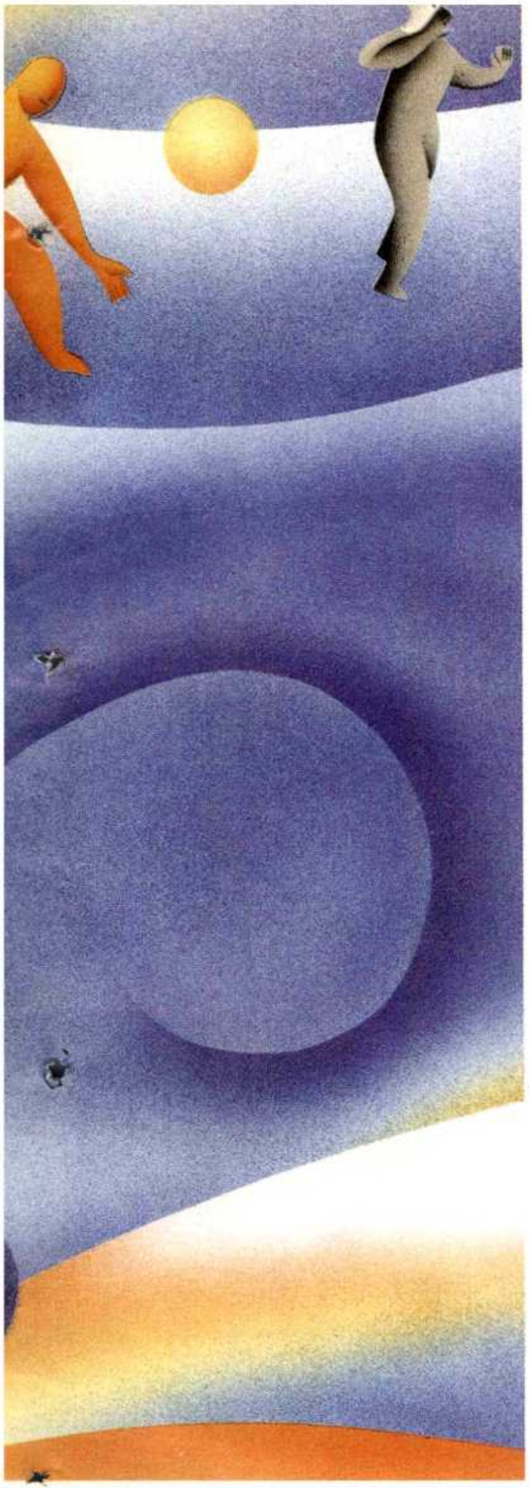
Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib.

Rofecoxib may mask fever.

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone.This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of



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rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with rofecoxib for one year or longer.

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

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References:

1. Ehrich EW, Dallob A, De Lepeleire I et al. Characterization of rofecoxib as a cyclo-oxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999; 65(3):336-347.
2. Data on file, Merck Sharp & Dohme Limited.
3. Laine L, Harper S, Simon T et al. A randomised trial comparing the effect of rofecoxib, a cyclo-oxygenase-2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. *Gastroenterology* 1999;117:776-783.

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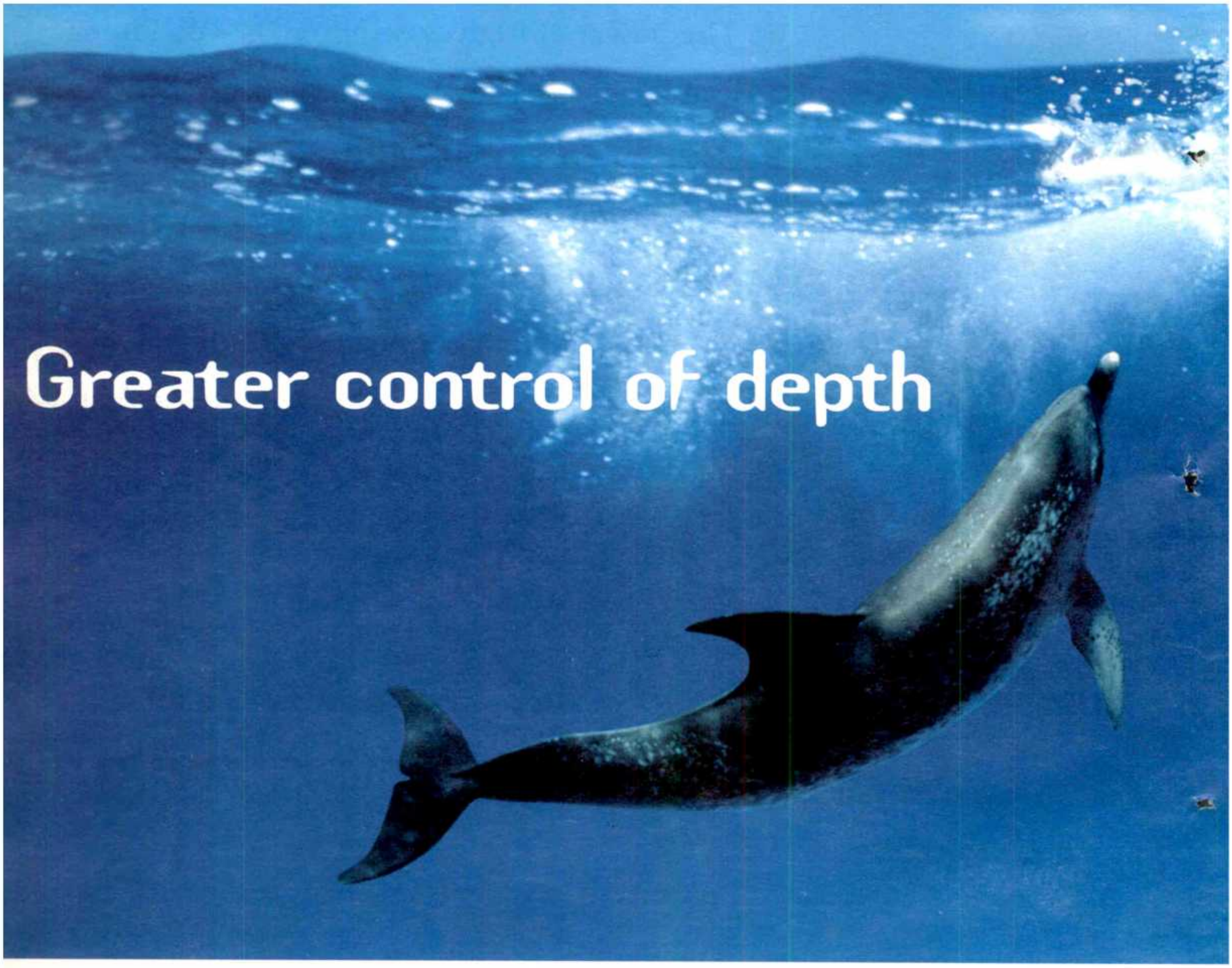

SUPRANE® (desflurane) PRESCRIBING INFORMATION
Presentation: Amber glass bottle containing 240ml desflurane, supplied as pure drug substance. Suprane is a volatile liquid for administration by inhalation. Store in an upright position at room temperature (25°C). **Indication:** Inhalation agent for induction and/or, maintenance of anaesthesia for inpatient and outpatient surgery in adults and maintenance of anaesthesia for inpatient and outpatient paediatric surgery. **Dosage:** Suprane should be administered by trained anaesthetists using a specific vaporiser designed for Suprane. MAC is age-specific and decreases with increasing age. *Induction.* Inspired concentrations of 4-11% of Suprane usually produce surgical anaesthesia in 2-4 minutes. Suprane is not recommended for paediatric induction. *Maintenance.* Surgical anaesthesia may be sustained with 2-6% Suprane when nitrous oxide is used concomitantly. Suprane at 2.5-8.5% may be required when administered using oxygen or oxygen enriched air. Concentrations of up to 18% Suprane have been administered for short periods of time, but if high concentrations are used with nitrous oxide, ensure that the inspired mixture contains a minimum of 25% oxygen. Concentrations of 1-4% in nitrous oxide/oxygen have been used successfully in patients with chronic renal/hepatic impairment. **Contraindications:** Suprane should not be used in patients in whom general anaesthesia is contraindicated, in patients with known hypersensitivity to halogenated agents, or in patients with known or genetic susceptibility to malignant hyperthermia. Suprane should not be used for induction in patients at risk of coronary artery disease or where increases in heart rate or blood pressure are undesirable. **Precautions:** Suprane is not recommended for paediatric induction, or for use in neurosurgical patients. Suprane may increase CSF or intracranial pressure in patients with space occupying lesions. A lower concentration is recommended for hypovolaemic, hypotensive and debilitated patients. Sensitivity hepatitis may be caused in patients previously sensitised by exposure to other halogenated anaesthetics. Suprane has been shown to trigger malignant hyperthermia. To minimise the risk of formation of carbon monoxide in rebreathing circuits, carbon dioxide absorbents should not be allowed to dry out. Suprane is not indicated during pregnancy or breast

and faster recovery

When compared with sevoflurane and isoflurane, Suprane has:

- lower solubility[1]
- faster wash in and wash out[1]
- more rapid emergence and recovery[2]

feeding. **Side effects:** Suprane may cause dose-dependent cardio-respiratory depression. Nausea and vomiting have been observed. Hepatitis may occur in patients sensitised by prior exposure to halogenated anaesthetics. In adult induction, cough, breath holding, laryngospasm, apnoea and salivation have been reported. Transient elevations in white blood cell count have been observed. Rare cases of malignant hyperthermia have been reported. No information exists on the effects of Suprane on the ability to drive or operate machinery. An adequate period, at least 24 hours, is needed to ensure full recovery. **Interactions:** Suprane potentiates commonly used muscle relaxants. Lower doses of Suprane are required in those receiving opioids, benzodiazepines, other sedatives, and nitrous oxide. **Overdose:** There is no experience of overdose in humans. Please consult Summary of Product Characteristics for recommendations in the case of overdosing. **Legal category:** POM. **Packs:** Suprane 240ml in amber glass bottles. **Basic NHS price:** £44.41 per bottle. **PL number:** 0116/0327. **PL holder:** Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk IP24 3SE. **Date of preparation:** December 1999.

® Denotes registered trademark.

References: 1. Eger E I. Anesth. Review. 1993;**20**:87-92. 2. Dupont I et al. Br J Anaesth. 1999;**82**:355-359.

Baxter Healthcare Ltd., Wallingford Road, Compton, Nr. Newbury, Berkshire. RG20 7QW. Tel: 01635 206000

Suprane®
desflurane

Precise control in
maintenance anaesthesia

SUP021/UK/0200

ESMERON

Presentation: 10 mg/ml rocuronium bromide in 5ml or 10ml vials as an aqueous solution for injection. **Other ingredients:** sodium acetate, sodium chloride, acetic acid to pH 4 and water for injections.
Uses: As an adjunct to general anaesthesia to facilitate endotracheal intubation during routine and rapid sequence induction, to provide skeletal muscle relaxation, during surgery. Esmeron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation.
Dosage and administration: Esmeron is administered intravenously as a bolus or as an infusion. See Summary of Product Characteristics for compatibilities.
Dosage is individualized taking into account method of anaesthesia, duration of surgery, possible interactions with other drugs and the patient's condition. Routine use of appropriate neuromuscular monitoring technique is recommended.
In adults: For short to long lasting surgical procedures:
Intubation: 0.6 mg / kg, Rapid sequence induction 1.0mg/kg,
Maintenance dose: 0.15 mg/kg, (reduce to 0.075mg - 0.1mg/kg for Long-term inhalational anaesthesia).
Continuous infusion: Loading dose 0.6 mg/kg, then infusion rate 0.3 - 0.6 mg/kg/hour or under inhalational anaesthesia 0.3 - 0.4mg/kg/hr. Continuous monitoring of block is essential.
(See Summary of Product Characteristics for advice for intensive care procedures, children, elderly, cirrhotic and overweight patients).
Contraindications Previous anaphylactic reactions to rocuronium or the bromide ion.
Precautions and warnings: Use under the supervision of experienced clinicians familiar with neuromuscular monitoring techniques. Ventilation is mandatory until adequate spontaneous respiration is restored. Dose levels above 0.9 mg/kg may increase heart rate which could counteract bradycardia produced by other anaesthetic agents or vagal stimulation. Hepatic and/or biliary tract disease, renal failure, prolonged circulation time and neuromuscular disease hypothermia and obesity may influence the effects of Esmeron. Severe electrolyte disturbances, altered blood pH or dehydration should be corrected when possible. Clinicians should be aware of the signs and symptoms of malignant hyperthermia
Effect on ability to drive or use machines: Using potentially dangerous machinery or driving are not recommended within 24 hours of full recovery.
Use in pregnancy and lactation: Esmeron should be given to pregnant or lactating women only when the benefits outweigh the risks. Dose in Caesarean section: 0.6mg/kg.
Side effects: Anaphylactic reactions are very rarely seen. No clinically significant tachycardia, hypotension or other clinical signs of histamine release have been reported.
Interactions: Other drugs may influence the effects of non-depolarizing NMBA's, including anaesthetics, other NMBA's, antibiotics and suxamethonium, diuretics, (-adrenergic blocking agents. See Summary of Product Characteristics for details.
Overdose: The patient should continue to be ventilated. When reversal fails ventilation must be continued until spontaneous breathing occurs.
Other Information: A dose of 0.6 mg/kg provides adequate intubation conditions within 60 seconds in nearly all patients, with a clinical duration of 30-40 minutes. General muscle paralysis is established within 2 minutes.
Package quantities: 50mg/5ml (12 vials) 100 mg/10ml (10 vials).
NHS Prices 50mg x12 vials - £38.78 100mgx10 vials - £64.63 Legal Category POM Product Licence Number 3524/0025
Further information is available from Organon Teknika Limited, Cambridge Science Park, Milton Road, Cambridge CB4 OFL

Oct 1999

organonteknika Boseind 15, 5281 RM Boxtel, The Netherlands, tel. +31 (0) 411 65 49 11, fax +31 (0) 411 65 42 01
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Rapid relaxation gets the applause...

...then predictable recovery steals the show.

An outstanding safety profile in all procedures.

Esmeron has now been used with confidence in over 35 million patients. This confidence is the result of its outstanding clinical profile:

Rapid onset

Esmeron at a dose of 0.6 mg/kg ensures control of the airway within one minute in 95% of patients. Its onset time is faster than that of all available non-depolarizing neuromuscular blocking agents.[1]

Predictable recovery

Esmeron's spontaneous recovery index is relatively constant, following either single or multiple bolus doses or after use as a long-lasting intravenous infusion.[2,3]

Stable hemodynamic profile

"In contrast to atracurium, mivacurium and tubocurarine, administration of Esmeron caused no significant changes in plasma histamine concentrations or in hemodynamic state at any time."[4]

For full details of this exceptional all-rounder, please contact your local Organon Teknika representative.

1. Puhringer et al. Anesth. Analg. 1992; 75: 37 - 40 **2.** Foldes et al. Exc Med Ams. 1990: 171 - 181 **3.** Sparr et al. Eur J Anaesth. 1994: 11(9): 63 - 65 **4.** Naguib et al. Br J Anaesth. 1995; 75: 588 - 592

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For more information: Organon Teknika bv, Boseind 15, 5281 RM Boxtel, telephone +31 (0)411 654911, telefax +31 (0)411 654201

Editorial Notices

Symposium on Intensive Care Issues

Leicester, May 26, 2000

The symposium will be held at the Glenfield Hospital Clinical Education Centre, Leicester.

The deadline for registration is May 15, 2000.

For further information and registration, please contact:

Mrs Julia Symons, Clinical Education Centre, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK.

Tel: +44 (0) 116 256 3603; Fax: +44 (0) 116 256 3334; E-mail: julia.symons@glenfield-tr.trent.nhs.uk

5th Congress of the European Resuscitation Council 'Resuscitation 2000'

Antwerp, June 1–3, 2000

Congress Director: Prof. Dr Leo Bossaert

For further information, registration and abstracts, please contact:

ERC secretariat, PO Box 113, 2610 Antwerp, Belgium.

Tel: +32 3 821 36 16; Fax: +32 3 828 48 82; E-mail: erc@uia.ua.ac.be; Website: http://www.erc.edu.

For hotel reservation and tours, contact:

Medicongress, Waalpoel 28/34, 9960 Assenede, Belgium.

Tel: +32 9 344 39 59; Fax: +32 9 344 40 10; E-mail: ERC2000@medicongress.com; Website: http://www.medicongress.com/erc.

*Pre-congress courses in BLS, AED, ALS, PLS on May, 29–31, 2000.

M.E.R.I.T. Centre Bradford Royal Infirmary, Bradford, UK – One day course in Spinal Endoscopy

Bradford, UK, June 9, 2000, September 15, 2000 and October 27, 2000

One day course with lectures, practical equipment demonstrations and observation of the technique in patients. Course material includes a comprehensive, practical guide to all aspects of the technique. Instrumentation is state-of-the-art, and it is anticipated that upon completion delegates will be in a position to consider setting up such a service in their own locality. On-going training will be offered.

Of interest to all those involved in the management and investigation of patients with back pain and sciatica as well as those involved with central neural blocks. Numbers of delegates strictly limited. Lunch will be provided.

For further information please contact:

Dr Jonathan Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford, BD9 6RJ.

Tel: +44 1274 364271/364253; Fax: +44 1274 366811; E-mail: merit.centre@mail.bradh-tr/northy.nhs.uk

Frontiers in Anesthesia

Allergy, Immunology, and Anesthetic Action
Ontario, June 10–12, 2000

The conference will take place at Queen's Landing Hotel, Niagara-on-the-Lake, Ontario, Canada.

For further information and registration, please contact:

Centre for Continuing Education, Tulane University Medical Center, 1430 Tulane Ave, TB 51, New Orleans, LA 70112, USA.

Tel: +1 800 588 5300 or +1 504 588 5466; Fax: +1 504 584 1779; E-mail: cme@mailhost.tcs.tulane.edu.

For further details and electronic registration, visit the web page: http://www.tmc.tulane.edu/anes/niagara/

World Paediatric Anaesthesia Meeting

Nova Scotia, June 14–16, 2000

The meeting will take place at the Westin Nova Scotian Hotel, Halifax, Nova Scotia, Canada.

For further information, please contact:

Dr. John G. Muir, Division of Paediatric Anaesthesia, IWK Grace Health Centre, 5850 University Avenue, Halifax, Nova Scotia, Canada B3J 3G9.

Fax: +902 428 2911. E-mail: wpam2000@is.dal.ca Visit our web site: www.dal.ca/wpam2000.

Therapeutic Applications of Leukocyte Filtration

London, July 7, 2000

The Hammersmith Hospital, Imperial College, London, UK, is pleased to stage a one-day workshop. This prestigious meeting is being organized by Professor Ken Taylor and Dr Terry Gourlay who have invited a guest panel of international speakers.

Topics presented include: Angioplasty Therapy for Acute Myocardial Infarction with Leukocyte Filtration; Filtration of Malignant Cells using Leukocyte Filtration on Cardiopulmonary Bypass; Leucofiltration of Cell Salvaged Blood; Techniques and Timing of Systemic Leukocyte Filtration on Cardiopulmonary Bypass; Leukocyte Depletion in Vascular Surgery; Leukocyte Tactics and Improved Patient Outcome After Extracorporeal Circulation; Leukocyte Filtration in Paediatric Cardiac Surgery; Systemic Leukocyte Filtration

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during Cardiopulmonary Bypass; Effects of Leukocyte Filtration of Blood Transfusion on Postoperative Complications; The Therapeutic Benefit of Depleting Blood Polymorthonuclear Cells from Patients with SIRS; Role of Leukodepletion in SIRS.

Abstracts are invited for poster presentations at this workshop. Abstract forms are available from the conference centre (address below). Prizes will be awarded to the best three abstracts.

Further details and registration forms are available from:

Jean Bryant, Manager, Wolfson Conference Centre, Imperial College of Science, Technology and Medicine, Hammersmith Hospital, Du Cane Road, London W12 ONN, UK.

Tel: +44 (0) 208 383 3117; Fax: +44 (0) 208 383 2428; E-mail: wcc@rpms.ac.uk

Edinburgh Anaesthesia Festival

Edinburgh, August, 23–25, 2000

Organized by the Department of Anaesthetics, Royal Infirmary of Edinburgh, to coincide with the 2000 Edinburgh International Festival of the Arts. The 3-day programme consists of lectures and discussion on current topics in anaesthesia. The lecturers are from all parts of the United Kingdom and represent leading opinions in their field.

For further information: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW. Tel: +44 131 536 3652; Fax: +44 131 536 3672; E-mail: anaes@ed.ac.uk

The Fifth Annual Symposium of the Association for Low Flow Anaesthesia

Ulm/Neu-Ulm/Germany, September 8–9, 2000

For further information, please contact:

Priv. Doz. Dr Uwe Schirmer, Priv. Doz. Dr Thomas Marx, Department of Cardiac Anaesthesia, University of Ulm, Steinhövelstr. 9, D-89075 Ulm, Germany.

Tel: +49 731 5021521; Fax: +49 731 5026757; e-mail: alfa2000@gmx.net; congress homepage http://www.uni-ulm.de/alfa2000.

XIX Annual Congress of the European Society of Regional Anaesthesia Joint Annual Congress with EuroPain 8th European Conference on Pain Research

Rome, Italy, September 20–23, 2000

The congress will be held in the Sheraton Hotel.

Abstract deadline is June 1, 2000.

For further information, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 5643; Fax: +032 2 346 5435;
E-mail: dionne@options.com.cy

Surfactant 2000

From Trier to Basle September 23–29, 2000

This is an international floating congress on the rivers Mosel and Rhine. All aspects of surfactant (basic science/clinical applications) will be addressed.

For further information, please contact:

Dr B. Lachmann, Department of Anesthesiology, Erasmus University Rotterdam, Postbox 1738, 3000 DR Rotterdam, The Netherlands.
Web site: http://www.floating-congress.vet.uu.nl

13th Annual Congress of the European Society of Intensive Care Medicine

Rome, Italy, October 1–4, 2000

For further information, please contact:

ESICM Congress Secretariat, 40 Avenue Joseph Wybran, B-1070 Brussels, Belgium.

Tel: + 32 2 559 0355; Fax: +32 2 527 0062; E-mail: public@esicm.org; Internet http://www.esicm.org

Dingle 2000 – Current Controversies in Anaesthesia and Perioperative Medicine

Dingle, County Kerry, Ireland, October 4–8, 2000

University College London Hospitals Centre for Anaesthesia announce a call for abstracts: there is an opportunity to submit work for poster presentation and selected finalists will be invited to give an oral presentation (prizes totalling £1000). Any research is acceptable provided it has not been published in any peer reviewed journal by the abstract deadline of 30 June 2000.

For further abstract and meeting registration details please contact:

Dr Monty Mythen, Centre for Anaesthesia, Room 103, 1st Floor Crosspiece, Middlesex Hospital, Mortimer Street, London, W1N 8AA, UK.

Tel: +44 20 7380 9477; Fax: +44 20 7580 6423;
E-mail: uch.acru@btinternet.com

European Academy of Anaesthesiology European Diploma in Anaesthesiology and Intensive Care

Part I (MCQ), October 7, 2000

(Endorsed by the European Board of Anaesthesiology (EBA) of the Union of European Medical Specialists (UEMS)

This examination will be held in English, French, German, Italian and Spanish in Athens, Barcelona, Berne, Budapest, Cluj-Napoca, Göttingen, Liège, Ljubjlana, London, Lund, Moscow, Oslo, Paris, Poznan, Riga, Rome, Tel Aviv, Uppsala and Vienna.

Regulations and application forms are available from:

Examinations Manager, European Academy of Anaesthesiology, London House, 243 Lower Mortlake Road, Richmond, Surrey TW9 2LS, UK.
Tel: +44 (0)208 940 6240; Fax: +44 (0)208 940 6262; E-mail: DEAA@compuserve.com; Home page: http://eaa-web.eu.org

The closing date for receipt of applications is May 31, 2000 (fee: £170)

Applications received after the closing date or unaccompanied by the full fee cannot be accepted and will be returned.

Wood Library-Museum's Quadrennial Laureate of the History of Anesthesia Prize

Members of the Editorial team of the *BJA* are pleased to announce that, Dr Thomas B. Boulton (UK) and Dr Norman A. Bergman (USA) are to be awarded the Wood Library – Museum's quadrennial Laureate of the History of Anesthesia Prize at the annual meeting of the American Society of Anesthesiologists in October 2000, in San Francisco.

We offer our hearty congratulations to Dr Boulton, and to the family of Dr Bergman, who unfortunately died recently.

St Bartholomew's Hospital Choral Society

Royal Albert Hall, London, UK, November 21, 2000

St Bartholomew's Hospital Choral Society celebrates the millennium and their 35th anniversary with the Royal Medical Benevolent Fund as their chosen Charity for their season 2000/2001.

Mahler's Symphony No. 8 'Symphony of a Thousand' with the Royal Philharmonic Orchestra, Royal Albert Hall, 21 November 2000.

It needs a *really* big choir, splendid orchestra, fine soloists and conductor. Six hundred singers are needed for this monumental work.

To participate contact the Barts Choir Honorary Secretary on:

Tel: +44 1628 664157.

Or to support, details available from:

The Royal Medical Benevolent Fund, 24 King's Road, Wimbledon, London SW19 8QN.

Tel: +44 20 8540 9194; Fax: +44 20 8542 0494;
E-mail: rm.bf@virgin.net

11th Congress, Western Pacific Association of Critical Care Medicine

Singapore November 29–December 3, 2000

This meeting will take place at the Westin Stamford and Westin Plaza, Singapore and is organized by the Society of Intensive Care Medicine (Singapore).

For further information, please contact:

11th WPACCM Congress Secretariat, Academy of Medicine, Singapore College of Medicine, Building 16, College Road, #01-01, Singapore 169854.
Fax: +65 225 5155; E-mail: monicaw@pacific.net.sg

19th Annual Symposium Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

San Juan, Puerto Rico, January 13–20, 2001

Free Papers will be accepted for oral and poster presentation in four categories: (i) monitoring; (ii) new pharmacological agents; (iii) interesting case reports; (iv) cardiopulmonary bypass technology. Abstracts forms are available upon request. The deadline for submission is November 1, 2000. Tuition will not be waived. Brochure available in June 2000.

For information and abstract forms contact: Helen Phillips, Box 1010, Mt. Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029-6574, USA.

Tel: +1 212 241 7630; Fax: +1 212 426 2009; E-mail: helen_phillips@smtplink.mssm.edu

2nd International Conference on Pain Control and Regional Anaesthesia

Jaipur, India, February, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA 4th Workshop 'Neural Blockades on Cadavers'

(European Society of Regional Anaesthesia)

Innsbruk, Austria, February 22–24, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESA 8th Annual Congress

(European Society of Anaesthesiologists)

Gothenburg, Sweden, April 10, 2001

Abstracts deadline: December 1, 2000

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

Anita Akabogy, Congress Department, MCN Medizinische Congress-organisation Nürnberg AG, Zerzabelshofstrasse 29, 90478 Nuernberg, Germany.

Tel: +49 911 393 16 10; Fax: +49 911 393 16 55; E-mail: akabogu@mcn-nuernberg.de; www: http://www. mcn-nuernberg.de

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg, June 13–16, 2001

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA XX Annual Congress

(European Society of Regional Anaesthesia)

Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

Awareness during Anesthesia—The 2000 *Anesthesiology* Journal-sponsored Symposium at the ASA Meeting

San Francisco, California, October 17, 2000, 9:00–12:30

The moderators will be Alex S. Evers MD (Washington University, St Louis) and Richard B. Weiskopf MD (University of California, San Francisco)

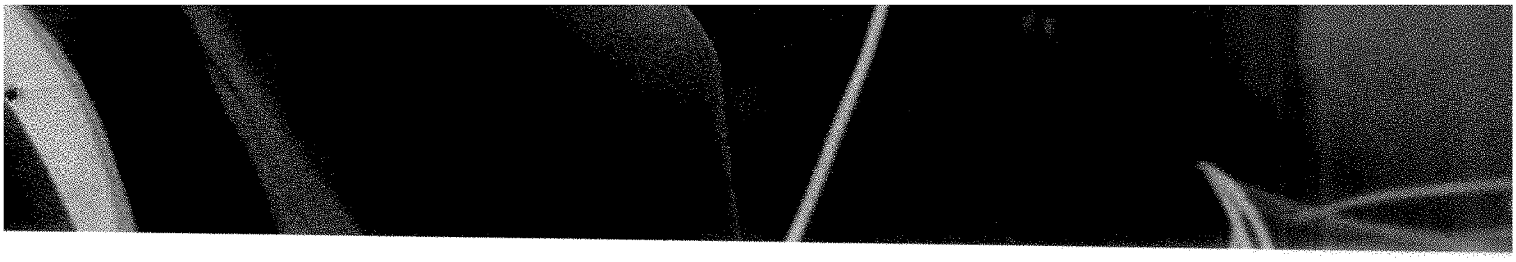
Awareness during anaesthesia is a potential problem of concern to clinicians and the public. There are clear cases of patients having been unintentionally awake during anesthesia and surgery and other cases for which 'awareness' was not as clearly delineated. 'Awareness' during anaesthesia and surgery can result in 'post-traumatic stress syndrome'.

This symposium will include invited speakers and a discussion session, as well as an opportunity to view selected abstracts. Abstracts in the following areas are considered appropriate for submission:

(i) epidemiology of 'awareness' during anaesthesia,
(ii) monitoring of depth of anaesthesia,
(iii) prevention of awareness during anaesthesia,
(iv) treatment of syndromes resulting from awareness during anaesthesia.

Abstracts should be submitted via the regular Annual Meeting procedures by April 1, 2000. *Online submission is available.* Abstracts requesting consideration for presentation at this symposium will undergo an additional review in addition to the standard ASA abstract review process. If you would specifically like your abstract considered for inclusion in the symposium, please check the special box that can be found on the cover letter/form which must accompany your submission. If you need abstract submission materials, please contact the American Society of Anesthesiologists:

American Society of Anesthesiologists, 520 N. Northwest Highway, Park Ridge, IL 60068–2573, USA.
Tel: +1 847 825 5586; Fax: +1 847 825 1692;
E-mail: mail@ASAhq.org Web site: http://www.asahq.org



Soft landing

They say anesthesia is like flying an airplane.
Taking off and landing are the riskiest phases.
Landing your patient softly in recovery
will never be routine.

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McMaster University
Hamilton, Canada

Cardiac Anaesthesia Fellowship

Applications are invited for a Cardiac Anaesthesia Fellowship at Hamilton Health Sciences Corporation, a tertiary regional cardiac centre serving an area from the Niagara Pennisula to the Bruce Peninsula as well as Northwestern Ontario. Annual cardiac surgical volume is over 1,300, providing a full range of cardiac surgical procedures.

Further information is available on the website:

http://www-fhs.mcmaster.ca/anaesthesia/education
or from Mrs Mary Gahagan, Office of the Chair,
Department of Anesthesia, McMaster University,
HSC-2U1, 1200 Main St W, Hamilton,
Ontario, Canada L8N 3Z5
Tel: 01-905-521-2100 ext. 75166
Fax: 01-905-523-1224
E-mail: gahaganm@fhs.mcmaster.ca

I S M E T T*

HEART/LUNG TRANSPLANT ANESTHESIA AT UPMC PALERMO

**(l'Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione)*

The University of Pittsburgh Department of Anesthesiology/CCM seeks attending anesthesiologists with fellowship training (or equivalent), for clinical O.R. care of heart/lung transplant recipients in Palermo, Italy. Exciting joint venture of UPMC Health System and the Italian Government. Position involves full time faculty appointment (all ranks) at the University of Pittsburgh, as well as an extremely attractive salary, benefits, and relocation allowance.

Send curriculum vitae and references to:

Leonard Firestone, M.D.
Safar Professor and Chairman
Department of Anesthesiology/CCM
University of Pittsburgh
A-1305 Scaife Hall
Pittsburgh, PA 15261
Fax: (412) 648-1887
E-mail: firestone@anes.upmc.edu

SOCIETY FOR AIRWAY MANAGEMENT

ANNUAL SOCIETY MEETING
WITH HANDS-ON WORKSHOPS

JUNE 2 – 4, 2000

LOEWS LE CONCORDE
Quebec City, Canada

Ulrich Braun, M.D., President
Program Chairman, D. John Doyle, M.D., Ph.D.

The Society For Airway Management (SAM) has been formed with the charter of improving airway management in adults and pediatrics, through research and education. Anesthesiologists, critical care specialists, emergency medicine physicians, otolaryngologists and CRNA's should attend. All aspects of the difficult airway will be covered including special cases pertinent to otolaryngologists and emergency medicine physicians. Hands-on workshops, taught by members of the distinguished faculty, will include training in the following: Adult & Pediatric Fiberoptic Intubation, Lung Isolation, Rigid Fiberoptic Laryngoscopy, Direct Laryngoscopy, Tracheal Light Wand, COPA, LMA, Airway Nerve Block, Combitube and VETT, Cricothyrotomy and Jet Ventilation, Retrograde Intubation, Rigid Bronchoscopy, Rigid Laryngoscopy and Airway Tube Exchangers. For more information or brochure contact:

MMC/UCI Center for Health Education
2801 Atlantic Avenue
Long Beach, CA 90806
(562) 933-0100 or
(562) 933-0101 FAX / britchie@memorialcare.org

Meeting Announcement

TEMPERATURE AND ACUTE CARE

Chaired by: Dr Mahesh Shah

Thursday, 29 June 2000
Rupert Beckett Lecture Theatre, University of Leeds

Thermoregulation and Anaesthesia
Dr Charles Deakin, Southampton

Effects of Temperature Changes on Organ Systems
Dr Angus Crossley, Derby

Temperature Regulation in the Critically ill Patient
Dr Andrew T Cohen, Leeds

Techniques to Regulate and Measure Temperature
Dr Bryn Baxendale, Nottingham

Temperature Care in the Accident and Emergency Dept
Mr Paul Grout, Hull

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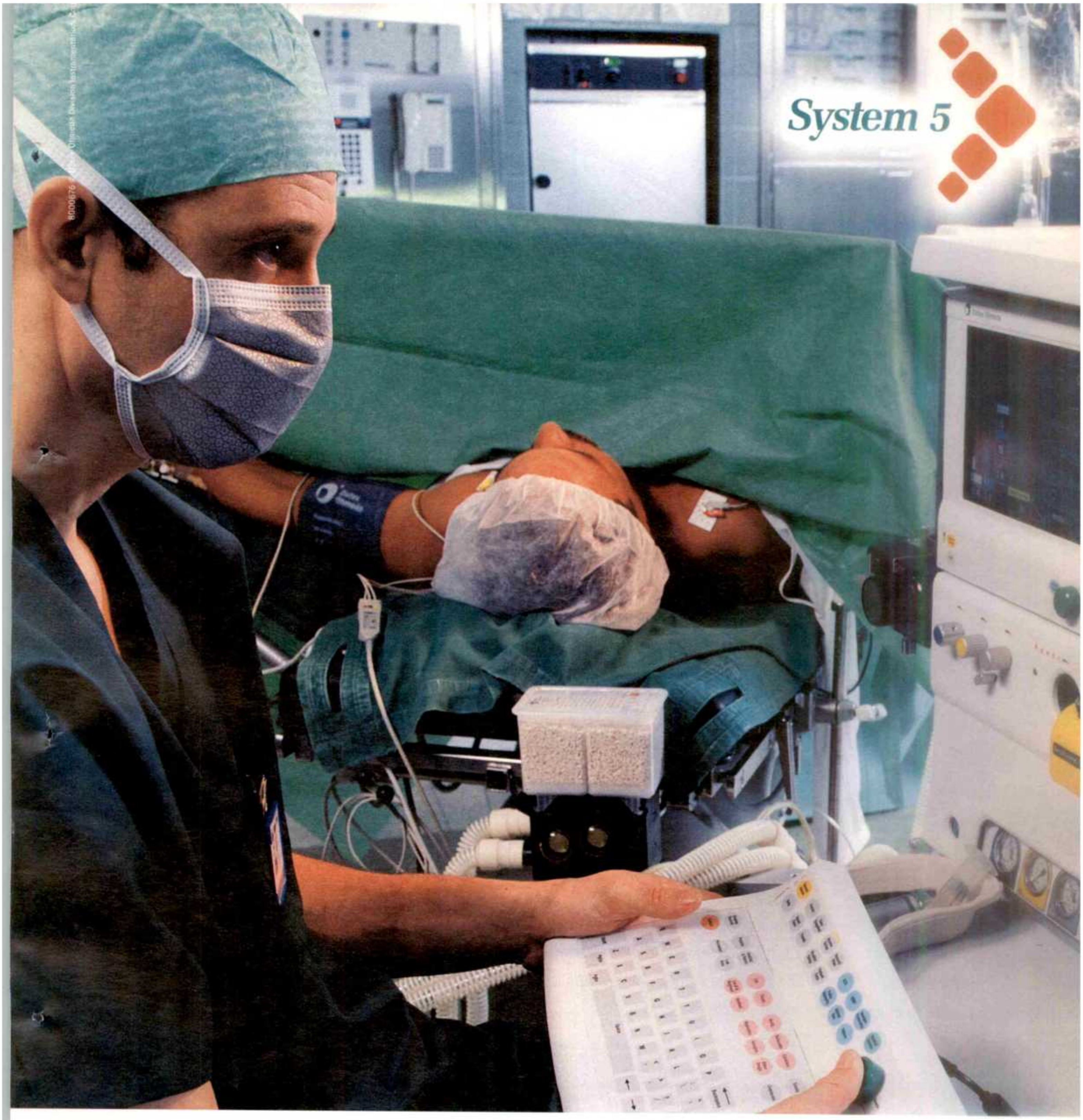

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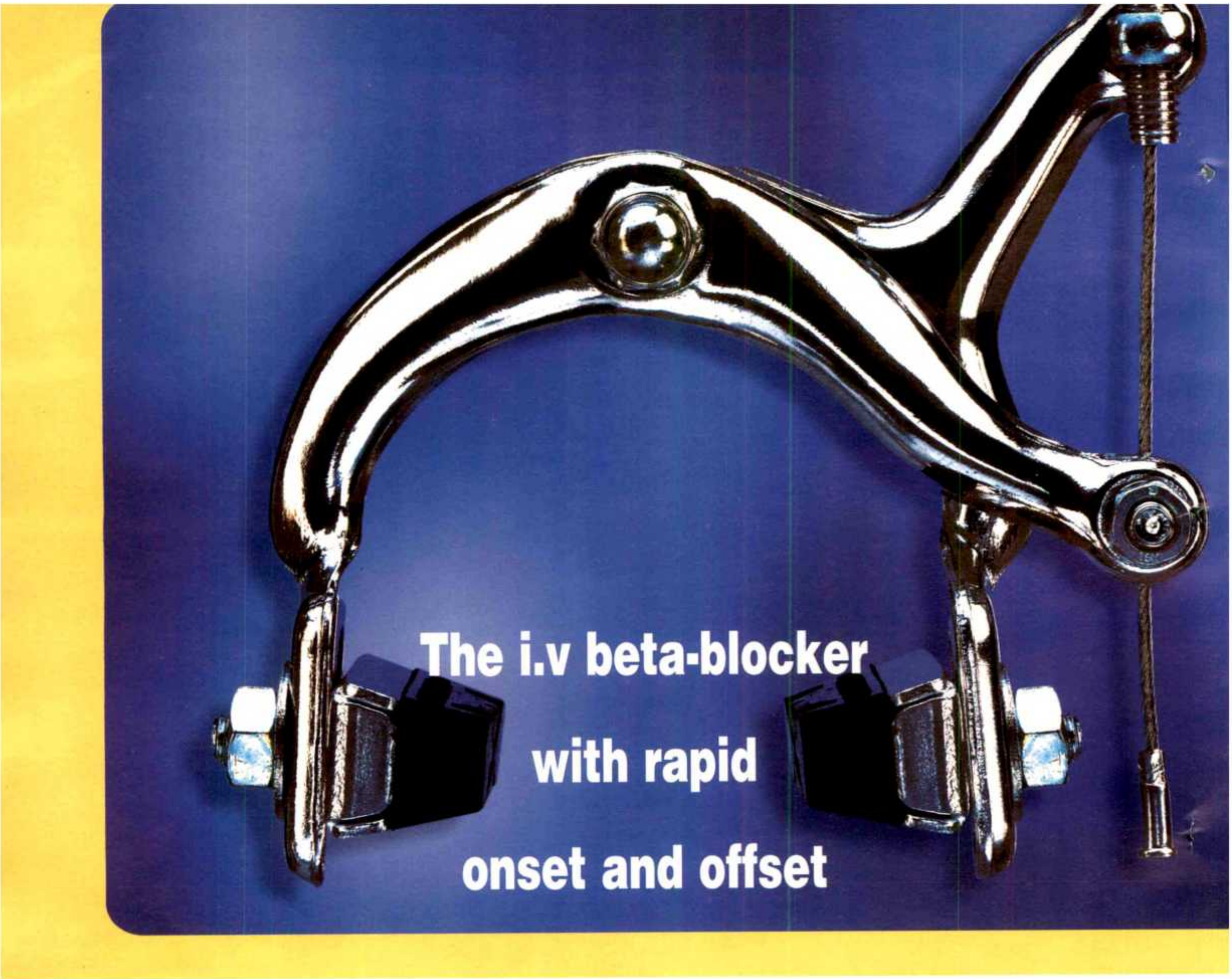

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Editorial I

Opioids in paediatric cardiac anaesthesia

In the last decade or so, informed opinion regarding the optimal timing of corrective surgery for infants with symptomatic congenital heart disease has undergone a highly significant revolution. Rather than the previous strategy of initial palliation followed by correction in early childhood, current 'best practice' now usually results in primary repair within weeks of birth. This radical change in surgical practice, together with an improved understanding of neonatal cardiorespiratory pathophysiology, has required paediatric cardiac anaesthetists to re-examine critically their anaesthetic techniques for neonates and young infants. Relative acceptance of peroperative haemodynamic instability has been replaced by an appreciation that it is only against a background of cardiovascular stability that appropriate manipulations of cardiac output and systemic and pulmonary vascular resistances can achieve optimization of perfusion and oxygenation.

This basic requirement for cardiovascular stability during cardiac anaesthesia has resulted in the widespread use of highly potent opioids, as their administration can substantially reduce the neurohormonal response to surgical stress and cardiopulmonary bypass (CPB).[1] High concentrations of circulating catecholamines peroperatively can cause significant postoperative myocardial dysfunction, due to an increase in ventricular afterload, adrenergic signal transduction failure, and exacerbation of reperfusion injury.[2–4] Experimentally, the neonatal animal appears particularly susceptible to catecholamine-induced myocardial injury.[5,6] Moreover, clinical studies have shown that neonates having cardiac surgery who die in the postoperative period often demonstrate higher hormonal and metabolic responses during the intra- and post-operative periods compared with 'matched' survivors.[1,7] However, although some elevation of circulating stress hormones is a normal adaptive response, it remains uncertain at what level this becomes detrimental. Thus, whilst blunting the extremes of the stress response appears a laudable aim, complete elimination is probably undesirable. It is likely that sick neonates with congenital heart disease are at least partially dependent on their relatively high levels of sympathetic stimulation and endogenous catecholamines for maintenance of their cardiac output.

It is unsurprising, therefore, that a high dose of a potent opioid usually forms a major part of most cardiac anaesthetics. However, the term "high dose" is open to varying interpretation, as there has been very little work to suggest what is the optimum dose of drug to use in this situation. The study by Duncan and colleagues reported in this issue of the journal attempts to answer this question.[8] They used five different doses of fentanyl in their study, and demonstrated that increasing the dose of fentanyl to 50 μg kg^{-1} or above appears to confer no additional benefit, in terms of reduction of stress hormone concentrations, compared with that produced by fentanyl 25 μg kg^{-1}. These results are comparable to those demonstrated in adults undergoing coronary artery surgery, who were given a high dose of fentanyl or sufentanil.[9] Here also, no evidence was found of a dose–response relationship between suppression of the haemodynamic and hormonal stress response and the opioid dose, when fentanyl was given in a dose of 50 μg kg^{-1} or more.

In contrast to previous studies, this study concentrated solely on the pre-CPB period. This has obvious advantages for data collection, though at first glance it would appear to restrict the overall clinical applicability of their results. However, as the authors have remarked, it is illogical to treat the pre-CPB, CPB and post-CPB periods in the same way, as anaesthetic requirements will vary significantly between the various phases of the operation.[10] The concentration in vessel-rich tissues of any drug that is given by a single bolus injection before surgery commences will decrease significantly during CPB due to haemodilution, drug sequestration, and changes in protein binding. Furthermore, fentanyl has a marked tendency to bind to the surfaces of the CPB circuit.[11] Hence, additional opioid will be required during the CPB period. As the authors readily admit, one other complicating factor separates out this study from all others: their time from the induction of anaesthesia (IA) to the initiation of CPB was only 35 to 60 min. Many other centres will have a longer IA–CPB time than this, so that significant redistribution of fentanyl from vessel-rich to vessel-poor tissues will have occurred by the time of sternotomy, if the drug is given soon after induction of anaesthesia. Hence, it may be prudent to delay, at least

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partially, the administration of fentanyl until just before surgery commences.

Clinical studies in adults,[9] children[12 13] and infants[14] have shown that no particular dose or plasma concentration of opioid reliably and completely controls the haemodynamic and hormonal responses to noxious stimuli in all patients. The data produced by Duncan and colleagues tends to corroborate these previous findings, and the authors confirm that there is no advantage to be gained in increasing the dose of fentanyl above 50 μg kg^{-1}.[8] It would appear, therefore, that some autonomic and endocrine responses are not susceptible to opioid receptor agonism, though animal studies using fentanyl 3000 μg kg^{-1} suggest that surgical anaesthesia may be theoretically possible at extremely high plasma concentrations.[15] Moreover, as high doses of opioids may induce acute tolerance,[16] it would appear reasonable to use a more moderate dose, together with other anaesthetic agents or vasoactive drugs as indicated. The combination of a high-dose opioid with a low dose of a potent inhalational anaesthetic agent,[17] nitrous oxide[12] or a benzodiazepine[18] appears to provide a better suppression of the stress response than giving a high dose of opioid alone. Duncan and co-workers have demonstrated that fentanyl 25 μg kg^{-1}, when administered in conjunction with 0.5% isoflurane, is sufficient to ablate the stress response in most patients for at least 60 min.[8]

Are there any problems associated with giving an unnecessarily high dose of opioid? Respiratory depression and excessive sedation in the postoperative period may be a problem if fentanyl is given in very high dosage to infants, but that argument is not applicable if the newer opioids such as alfentanil and remifentanil, which have much shorter context-sensitive half times, are used. Alfentanil and remifentanil both have to be given by infusion, an advantage when, as discussed above, the opioid dose needs to be tailored to the different phases of the operation. Moreover, the tendency of alfentanil and remifentanil to adhere to the surfaces of the CPB circuit is less marked than that of fentanyl, and their pharmacokinetics during and after CPB are much more predictable.[19 20] Hence, other than being relatively cheap, fentanyl has no particular advantages over its more modern derivatives. However, even though alfentanil is about twice the price of an equipotent dose of fentanyl, and remifentanil about twice the price of alfentanil, the relative cost of any of these drugs compared with the overall cost of cardiac surgery remains insignificant. Although there are no significant differences between these drugs in terms of their acute pharmacodynamic effects, their pharmacokinetic profiles are dissimilar, and the continued use of fentanyl in cardiac anaesthesia often owes more to habit than to logic.

Another reason given by Duncan and colleagues for advocating the use of a minimum effective dose of opioid, rather than a dose in excess of that required, is the effect that opioids have on the immune system.[8] Although there is no direct evidence that peroperative administration of a high dose of a short-acting opioid produces clinically significant postoperative immune suppression, the potential for such drugs to produce a profound alteration in normal immune system function seems undeniable.[21] Another reason, perhaps, for using a short-acting opioid is that it does not have a tendency to sequester in adipose tissue. Whichever potent opioid is used peroperatively, postoperative analgesia for the majority of patients is conventionally provided by morphine, which not only is cheap, but also allows a smoother transition to the resumption of spontaneous respiration by the patient. However, patients requiring postoperative suppression of neuro-hormonal activation, such as those with severe pulmonary hypertension, may benefit from a prolongation of their potent opioid infusion until resolution of their problem.

Duncan and colleagues have established that, when used in conjunction with 0.5% isoflurane, the optimum pre-CPB dose of fentanyl for infants is between 25 and –50 μg kg^{-1}.[8] Moreover, the data from their study can be used, in conjunction with comparative opioid potency data,[22 23] to predict the required dose of other potent opioids. Further information as to whether the opioid dose administered has been sufficient to ablate the patient's stress response can be gleaned by monitoring of both haemodynamic parameters and, in the pre-CPB phase at least, blood glucose concentrations. Duncan and colleagues confirm previous observations made on infants having non-cardiac major surgery[24] that suggested that the blood glucose concentration provides a clinically useful contemporaneous quantification of the patient's stress response. Unfortunately, the inevitable increase in glucose concentrations during and after CPB, which may occur in the absence of other neuro-hormonal activation, precludes this method being applicable throughout the procedure.

Although it is now possible to administer extremely high doses of opioids to infants having cardiac surgery without any danger of provoking excessive postoperative sedation or respiratory depression, the study by Duncan and colleagues in this issue of the journal[8] has demonstrated that there appears to be little reason for doing so. Their paper provides us with the data that will enable us to prevent our patients mounting an excessive neuro-hormonal stress response, without our having to administer a disproportionate dose of opioid. Although regional anaesthesia may offer ablation of the stress response without immune suppression,[25] the technical difficulties inherent in placing thoracic epidurals in infants about to be heparinized make this technique unlikely to become the method of choice for the foreseeable future. Hence, further studies examining the relative efficacy of the newer opioids in modulating the neuro-hormonal stress responses of infants before, during and after CPB are now required.

P. D. Booker
Royal Liverpool Children's NHS Trust
Eaton Road
Liverpool L12 2AP
UK

References

1 Anand KJS, Hickey PR. Halothane–morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. *New Engl J Med* 1992; **326**: 1–9

2 Hajjar RJ, Muller FU, Schmitz W, Schnabel P, Bohm M. Molecular aspects of adrenergic signal transduction in cardiac failure. *J Mol Med* 19 1998; **76**. 747–55

3 Movsesian MA. Beta-adrenergic receptor agonists and cyclic nucleotide phosphodiesterase inhibitors: shifting the focus from inotropy to cyclic adenosine monophosphate. *J Am Coll Cardiol* 1999; **34**: 318–24

4 Caspi J, Coles JG, Benson LN, *et al.* Effects of high plasma epinephrine and Ca^{2+} concentrations on neonatal myocardial function after ischemia. *J Thorac Cardiovasc Surg* 1993; **105**: 59–67

5 Caspi J, Coles JG, Benson LN, Herman SL, Act JA, Wilson GJ. Heart rate independence of catecholamine-induced myocardial damage in the newborn pig. *Pediatr Res* 1994; **36**: 49–54

6 Caspi J, Coles JG, Benson LN, *et al.* Age-related response to epinephrine-induced myocardial stress. A functional and ultrastructural study. *Circulation* 1991; **84**: III394–99

7 Anand KJS, Hansen DD, Hickey PR. Hormonal-metabolic stress responses in neonates undergoing cardiac surgery. *Anesthesiology* 1991, **73**: 661–70

8 Duncan HP, Cloote A, Weir PM, *et al.* Reducing stress response in the prebypass phase of open heart surgery in infants and young children: a comparison of different fentanyl doses. *Br J Anaesth* 2000; **84**: 556–64

9 Philbin DM, Rosow CE, Schneider RC, Koski G, D'Ambra MN. Fentanyl and sufentanil anesthesia revisited: how much is enough? *Anesthesiology* 1990; **73**: 5–11

10 den-Hollander JM, Hennis PJ, Burm AGL, Vletter AA, Bovill JG. Pharmacokinetics of alfentanil before and after cardiopulmonary bypass in pediatric patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 1992; **6**: 308–12

11 Gedney JA, Ghosh S. Pharmacokinetics of analgesics, sedatives and anaesthetic agents during cardiopulmonary bypass. *Br J Anaesth* 1995; **75**: 344–51

12 Crean P, Koren G, Goresky G, Klein J, MacLeod S. Fentanyl–oxygen versus fentanyl–N_2O/oxygen anaesthesia in children undergoing cardiac surgery. *Can Anaesth Soc J* 1986; **33**: 36–40

13 Moore RA, Yang SS, McNicholas KW, Gallagher JD, Clark DL. Hemodynamics and anesthetic effects of sufentanil as the sole anesthetic for pediatric cardiovascular surgery. *Anesthesiology* 1995, **62**: 725–31

14 Hickey PR, Hansen DD. Fentanyl– and sufentanil–oxygen–pancuronium anesthesia for cardiac surgery in infants. *Anesth Analg* 1984; **63**: 117–24

15 Stanley TH, Bailey PL. Fentanyl & sufentanil anaesthesia revisited: establish an effective plasma concentration and achieve it at the right time. *Anesthesiology* 1991; **74**: 388–9

16 Arnold JH, Truog RD, Scavone JM, Fenton T. Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. *J Pediatr* 1991; **119**: 639–43

17 Ramsay JG, DeLima LGR, Wynands JE, O'Connor JP, Ralley FE, Robbins GR. Pure opioid versus opioid-volatile anesthesia for coronary artery bypass graft surgery: a prospective, randomized, double-blind study. *Anesth Analg* 1994; **78**: 867–75

18 Barankay A, Richter JA, Henze R, Mitto P, Spath P. Total intravenous anesthesia for infants and children undergoing correction of tetralogy of Fallot: sufentanil versus sufentanil–flunitrazepam technique. *J Cardiothorac Vasc Anesth* 1992; **6**: 185–9

19 Davis PJ, Wilson AS, Siewers RD, Pigula FA, Landsman IS. The effects of cardiopulmonary bypass on remifentanil kinetics in children undergoing atrial septal defect repair. *Anesth Analg* 1999; **89**. 904–8

20 Fiset P, Mathers L, Engstrom R, *et al.* Pharmacokinetics of computer-controlled alfentanil administration in children undergoing cardiac surgery *Anesthesiology* 1995; **83**: 944–55

21 Webster NR. Opioids and the immune system *Br J Anaesth* 1998; **81**: 835–6

22 Glass PS, Iselin CIA, Goodman D, Delong E, Hermann DJ. Determination of the potency of remifeantanil compared with alfentanil using ventilatory depression as the measure of opioid effect. *Anesthesiology* 1999; **90**: 1556–63

23 Jhaveri R, Joshi P, Batenhorst R, Baughman V, Glass PSA Dose comparison of remifentanil and alfentanil for loss of consciousness. *Anesthesiology* 1997; **87**. 253–9

24 Wolf AR, Doyle E, Thomas E. Modifying infant stress responses to major surgery; spinal vs extradural vs opioid analgesia. *Paediatr Anaesth* 1998; **8**: 305–11

25 Moon MR, Luchette FA, Gibson SW, *et al.* Prospective, randomized comparison of epidural versus opioid analgesia in thoracic trauma. *Ann Surg* 1999; **229**: 684–91

Editorial II

Off-pump coronary artery surgery and the brain

Off-pump coronary artery bypass grafting (CABG), which is surgery on a beating heart without the support of cardiopulmonary bypass (CPB), is currently attracting a lot of interest.[1–7] In this issue of the journal a study by Watters and colleagues[1] suggests that off-pump CABG surgery results in less cerebral embolic load than when the surgery is undertaken with CPB and should, therefore, result in less brain damage. This editorial outlines the reasons for the traditional use of CPB for CABG surgery and the attractions of conducting surgery 'off-pump'. In particular, it will discuss the reasons why CPB may cause brain damage and why off-pump CABG surgery should result in less injury. It will explain the importance of the study by Watters and colleagues[1] and why it should be interpreted with caution. Finally, there is a plea for randomized designs to be used in all future studies of CPB versus off-pump CABG surgery

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CABG surgery and CPB

The original motivation for developing CPB more than 45 yr ago was to allow the surgical treatment of congenital heart conditions and, subsequently, heart valve disease. Although CPB continues to be used for these purposes, it is currently used far more frequently for CABG surgery and every year it is used in hundreds of thousands of patients worldwide. CPB allows cardiac and pulmonary functions to be supported mechanically whilst the heart is isolated from the circulation by aortic cross-clamping and is rendered asystolic by cardioplegia or at least relatively stilled by ventricular fibrillation. The surgeon can then anastomose venous or arterial conduits to coronary arteries in a quiet and bloodless field, secure in the knowledge that the patient's life is supported by CPB.

Off-pump CABG surgery

Why then is there now such interest in undertaking CABG surgery without CPB on a beating heart? Certainly, off-pump CABG surgery is neither for the timid surgeon nor for the faint-hearted anaesthetist. The surgeon has to perform coronary anastomosis in a bloody field and often with less than ideal exposures. Moreover, surgery is performed on a beating heart, albeit with the aid of instruments developed to stabilize the coronary artery, and with the knowledge that the dependent myocardium may be becoming more ischaemic with every extra minute taken. For the anaesthetist, gone is that golden hour and more when one's mind could drift as the patient's circulation and gas exchange were supported by CPB. Instead, the anaesthetist has to watch as the surgeon, using skills seemingly learnt from professional wrestlers, locks the heart into very unnatural positions in which it would seem most unlikely that there could be any cardiac output. Unsurprisingly, cardiovascular collapse can ensue rapidly and ventricular fibrillation can occur in a blink of the eye. Such surgery demands an extremely high level of vigilance on the part of the anaesthetist and the ability to quickly support the circulation pharmacologically or to defibrillate the heart. To do such things might seem a strange form of professional masochism or machismo. However, anaesthetists and surgeons are motivated to avoid CPB by the promise of lower morbidity and less use of resources.

Without CPB, a perfusionist is not required and there is no expenditure on the disposables for the CPB circuit and oxygenator. Presently, these savings are somewhat illusory as, in our unit at least, we have not reached the stage where off-pump surgery is undertaken without a CPB circuit being primed and ready to use along with a perfusionist on standby within the theatre suite. CPB savings are offset by the not inconsiderable expense of the special retractors that are required to allow fixation of the coronary artery during anastomosis. Furthermore, not all patients have a pattern of coronary artery disease that is suitable for off-pump CABG surgery. However, some savings can be made if the off-pump surgery is undertaken on the first patient and the CPB circuit is then used for a subsequent case. A more tangible saving is that off-pump surgery takes less operating time,[2–4] and this might allow greater throughput of patients. Even more attractive is that the time required in the intensive care unit, and the total hospital stay, could be reduced,[3–5] probably through a reduction in complications.[4 7] CABG surgery is associated with many serious complications that are ascribed to CPB,[3 4 7] including dysfunction of the cardiovascular, pulmonary, renal, coagulation and inflammatory systems and, of particular importance to this editorial, brain damage.

Brain damage and CABG surgery

Overt neurological damage such as stroke is relatively rare, with an incidence of about 3% in patients having CABG surgery using CPB.[8] However, more subtle neurological deficits, such as primitive reflexes, ataxia and sensory loss, can occur in more than 60% of patients,[9–11] and for this reason these are increasingly being used as measures of cerebral outcome.[10–12] Brain damage can also be measured by changes in cognition. At about 1 week after surgery, the incidence of cognitive deficits can be as high 90%.[9 11] Whilst some of these deficits signal cerebral injury, many represent background noise as a result of pain, analgesic drugs and fatigue resulting from disturbances of sleep. A far better signal-to-noise ratio is obtained about 1–3 months after surgery, when the incidence of cognitive decline can be as high as 50%[11] and, importantly, the deficits are most likely permanent. Clearly, brain damage is associated with CABG surgery and the manifestations are wide.

Aetiology

Cerebral hypoperfusion during CPB has long been believed to be a cause of cerebral damage. Indeed, Croughwell and colleagues have found a weak association between a global estimate of cerebral hypoperfusion–jugular bulb oxyhaemoglobin desaturation–and cognitive decline.[13] Desaturation occurred during the rewarming phase of hypothermic CPB, and probably represents an imbalance between cerebral oxygen supply and demand. Moreover, cerebral hypoperfusion may not be confined to CPB as prolonged periods of jugular bulb desaturation have been found to occur in many patients during the early postoperative period.[14]

Multifactorial. Recently, a number of other mechanisms have been put forward, including genetic predisposition,[15] nitric oxide,[16] glutamate excitotoxicity[16] and inflammation.[17] As there appears to be more than one smoking gun, it seems likely that the aetiology is multifactorial.[12] However, one factor that stands out is cerebral embolization.

Macroemboli are most probably the cause of overt neurological injury such as stroke and can arise from intracardiac air or thrombus, atheromatous plaques dislodged from the aorta during clamping and cannulation, and calcific debris from valve excision. For these reasons, there is a very high incidence of stroke associated with combined heart valve and CABG surgery.[18]

Microemboli, which can be gaseous or particulate, are probably the cause of cognitive and subtle neurological deficits. Transcranial Doppler ultrasound imaging of the middle cerebral artery can be used to quantify the numbers of emboli reaching the brain,[19 20] but it cannot determine their nature. Gaseous microemboli are generated in the CPB circuit as a result of direct interfacing between blood and gas, and by the interventions of the perfusionist.[19] Microparticulate emboli can arise from spallation of the inner surface of pump tubing, especially that made with silicon, by roller pumps; lipids in blood salvaged from the pericardium;[21] fracturing of atheromatous plaques by cannulation or cross-clamping of the aorta; and scouring of an atheromatous intima by the outflow from the aortic pipe.[3] Crucially, regardless of their nature, the number of cerebral microemboli measured by transcranial Doppler ultrasound is related to cerebral damage as measured by the cognitive outcome.[20]

Watters and colleagues' study[1]

One of the most obvious ways of reducing the generation of microemboli during CABG surgery would be to avoid CPB.[3] Indeed, using transcranial Doppler ultrasound in a small population of 20 patients, Watters and colleagues have found this to be exactly the case.[1] However, as they did not examine the neurocognitive outcome, it cannot be determined whether the lower embolic load was associated with less cerebral injury. This limitation notwithstanding, the findings of Watters and colleagues[1] are important as they give weight to the hypothesis of Murkin and colleagues that off-pump CABG should reduce cerebral injury by reducing the cerebral embolic load.[3]

Other evidence supporting the hypothesis that off-pump CAB surgery is less harmful comes from a study by Anderson and colleagues, which compared the cerebral effects of CPB and off-pump CABG surgery by measuring serum S100 protein.[22] This is released from astroglial cells after injury, and serum concentrations of the protein after stroke and head injury are prognostic of the cerebral outcome.[23 24] Anderson and colleagues found that concentrations of S100 protein were lower in patients having CABG surgery off-pump compared with those having CPB. However, although S100 protein concentrations are elevated during CPB, they have not been found to be highly specific with respect to the cognitive and neurological outcomes, and there may be reasons other than cerebral injury for its elevation.[12]

To find definitive answers, the outcome has to be examined using a robust study design. In a preliminary report of a study in progress, Murkin and colleagues have found a dramatic reduction in the incidence of cognitive dysfunction 3 months after surgery from 50% in patients undergoing CABG surgery with CPB to 5% in off-pump patients.[3] However, they used a non-randomized design. Patients having off-pump surgery had fewer mean numbers of coronary anastomoses than those with CPB (3.2 *vs* 1.1), and the authors were clearly comparing different populations. Patients with less coronary artery disease may well have less cerebrovascular disease and aortic atherosclerosis and so are less predisposed to cognitive decline. By contrast, Taggart and colleagues also compared cognitive outcome in patients undergoing CABG surgery with and without CPB, but they found no significant difference between the groups.[2] Again, non-randomization is the most important of several reasons why the study is inconclusive, and Murkin's commentary should be read along with the study.[25]

So, whilst the study by Watters and colleagues[1] indicates that off-pump CABG surgery is associated with less cerebral embolic load and that of Anderson and colleagues[22] implies that it is associated with less cerebral injury, the outcome studies by Taggart and colleagues[2] and Murkin and colleagues[3] are contradictory. Because all of these studies are methodologically flawed by a non-randomized design, it is still unclear whether avoiding CPB reduces cerebral morbidity from CABG surgery.

Conclusions

The putative benefits of off-pump CABG surgery for the brain remain incompletely investigated. Similarly, there has been no systematic, rigorous, scientific evaluation of the potential benefits of off-pump surgery for the heart, lungs, kidneys and the coagulation and inflammatory systems. Moreover, whether the equivalent quality of coronary anastomosis can be achieved during beating-heart surgery, as when using CPB, requires clarification. Without doubt, developing a new technique requires a major degree of commitment by both the surgeon and anaesthetist. Inevitably, there will be a learning curve before any new technique is mastered, and until it has been mastered there is little point in comparing the new with the standard method. However, that time must be fast approaching and future studies comparing CPB and off-pump CABG surgery should employ robust study designs to establish whether or not the hypothesized benefits of beating-heart surgery to the brain and other systems really exist. CABG surgery, using CPB, had long been established as standard clinical practice before randomized controlled trials confirmed its beneficial effects upon longevity in patients with certain patterns of coronary disease and ventricular function. Let us hope that this will not also be the case with off-pump CABG surgery and that early randomized controlled trials will be undertaken.

R. Peter Alston
Department of Clinical and Surgical Sciences
University of Edinburgh
Department of Anaesthetics
Royal Infirmary of Edinburgh
1 Lauriston Place
Edinburgh EH3 9YW
UK

References

1 Watters MPR, Cohen AM, Monk CR, Angelini GD, Ryder IG. Reduced cerebral embolic signals in beating heart coronary surgery detected by transcranial Doppler ultrasound. *Br J Anaesth* 2000; **84**: 629–31

2 Taggart DP, Browne SM, Halligan PW, Wade DT. Is cardiopulmonary bypass still the cause of cognitive dysfunction after cardiac operations? *J Thorac Cardiovasc Surg* 1999; **118**: 414–20

3 Murkin JM, Boyd WD, Ganapathy S, Adams SJ, Peterson RC. Beating heart surgery: why expect less central nervous system morbidity? *Ann Thorac Surg* 1999; **68**: 1498–501

4 Turner, WF. 'Off-pump' coronary artery bypass grafting: the first one hundred cases of the Rose City experience. *Ann Thorac Surg* 1999, **68**: 1482–5

5 Boyd WD, Desai ND, Del Rizzo DF, Novick RJ, McKenzie FN, Menkis AH. Off-pump surgery decreases postoperative complications and resource utilization in the elderly. *Ann Thorac Surg* 1999; **68**: 1490–3

6 Cartier R. Systematic off-pump coronary artery revascularization: experience of 275 cases. *Ann Thorac Surg* 1999; **68**: 1494–7

7 Cartier R, Bouchard D, Martineau R. Perioperative benefits of beating heart coronary surgery among patients with triple vessel disease. *Ann Chir* 1998; **52**: 801–6

8 Roach GW, Kanchuger M, Mangano CM, *et al.* Adverse cerebral outcomes after coronary bypass surgery. *N Engl J Med* 1996; **335**: 1857–63

9 Shaw PJ, Bates D, Cartlidge NEF, *et al.* Neurologic and neuropsychological morbidity following major surgery—comparison of coronary-artery bypass and peripheral vascular-surgery. *Stroke* 1987; **18**: 700–7

10 Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary-artery bypass-surgery: 2. Neurologic and cognitive outcomes. *J Cardiothorac Vasc Anesth* 1995; **110**: 349–62

11 Roach GW, Newman NF, Murkin JM, *et al.* Ineffectiveness of burst suppression therapy in mitigating perioperative cerebrovascular dysfunction. *Anesthesiology* 1999; **90**: 1255–64

12 Alston RP, Souter MJ. Cerebral sequelae of cardiac surgery. *Curr Opin Critical Care* 2000; in press

13 Croughwell ND, Newman MF, Blumenthal JA, *et al.* Jugular bulb saturation and cognitive dysfunction after cardiopulmonary bypass. *Ann Thorac Surg* 1994; **58**: 1702–8

14 Souter MJ, Andrews PJD, Alston RP. Jugular venous desaturation following cardiac surgery. *Br J Anaesth* 1998; **81**: 239–41

15 Newman MF, Laskowitz DT, Saunders AM, Grigore AM, Grocott HP. Genetic predictors of perioperative neurologic and neuropsychological injury and recovery. *Semin Cardiothorac Vasc Anesth* 1999; **3**: 34–46

16 Tseng EE, Brock MV, Kwon CC, *et al.* Increased intracerebral excitatory amino acids and nitric oxide after hypothermic circulatory arrest. *Ann Thorac Surg* 1999; **67**: 371–6

17 Abdul-Khaliq H, Blasig IE, Baur MO, Hohlfeld M, Alexi-Mesckhishvili V, Lange PE. Release of cerebral protein S-100 into the blood after reperfusion during cardiac operations in infants: Is there a relation to oxygen radical-induced lipid peroxidation? *J Thorac Cardiovasc Surg* 1999; **117**: 1027–8

18 Wolman RL, Nussmeier NA, Aggarwal A, *et al* Cerebral injury after cardiac surgery: identification of a group at extraordinary risk. *Stroke* 1999; **30**: 514–22

19 Taylor RL, Borger MA, Weisel RD, Fedorko L, Feindel CM. Cerebral microemboli during cardiopulmonary bypass: increased emboli during perfusionist interventions. *Ann Thorac Surg* 1999; **68**: 89–93

20 Pugsley W, Klinger L, Paschalis C, Treasure T, Harrison M, Newman S. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke* 1994; **25**: 1393–9

21 Brown WR. Moody DM, Challa VR. Cerebral fat embolism from cardiopulmonary bypass. *J Neuropathol Exp Neurol* 1999; **58**: 109–19

22 Anderson RE, Hansson LO, Vaage J. Release of S100β during coronary artery bypass grafting is reduced by off-pump surgery. *Ann Thorac Surg* 1999; **67**: 1721–5

23 Raabe A. Grolms C, Seifert V. Serum markers of brain damage and outcome prediction in patients after severe head injury *Br J Neurosurg* 1999; **13**: 56–9

24 Wunerlich MT, Ebert AD, Kratz T, Goertler M, Jost S, Herrmann M. Early neurobehavioral outcome after stroke is related to release of neurobiochemical markers of brain damage. *Stroke* 1999; **30**: 1190–5

25 Murkin JM. Is cardiopulmonary bypass still the cause of cognitive dysfunction after cardiac operations? Commentary. *J Thorac Cardiovasc Surg* 1999; **118**: 420–1

Editorial III

Qualitative research in health care

The standing of anaesthesia as a medical specialty has been underpinned by a long-standing commitment to its scientific foundations through sound research. This principle – that medical practice should be 'evidence based' – has recently received great emphasis. So-called 'levels of evidence' have been identified,[1] and clinical guidelines based on analyses of hierarchies of quantitative evidence are now the order of the day.[1–3] In a typical hierarchy of this kind, Level I is described as 'evidence from at least one well-designed randomized controlled trial' and 'systematic reviews with meta-analyses of the data from multiple randomized controlled trials (RCTs)'. Level II is designated as evidence from 'well-designed controlled trials without randomization' (II-1), 'well-designed cohort or case-control analytic studies' (II-2), and 'evidence from comparison between times and places with or without the intervention or dramatic results from uncontrolled studies' (II-3). The lowest level (III) is assigned to the 'opinions of respected authorities,

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based on clinical experience, descriptive studies or reports of expert committees'.[1] Formal methods of qualitative research are ignored, or at best, included by implication within level III.

What is qualitative research?

Qualitative research seeks an understanding of life events. As quantitative research might ask 'how many' patients failed to appear for their operations, qualitative research might try to determine 'why' those patients defaulted. One of the characteristics of qualitative research is its focus on natural (or 'real world'), rather than experimental or controlled, settings. Data are typically obtained from people actually participating in a given situation. The standard sampling methods of quantitative research have a recognized place in qualitative research, but often qualitative sampling endeavours to identify specific groups of people who have certain characteristics, live certain types of lives, or have certain points of view. Thus, in the above example, many of the patients who failed to arrive for their operations at the hospital in question may have done so because they were of a particular occupational group, and had the attributes, attitudes and constraints associated with that occupation. In qualitative research the emphasis is often local; specific conclusions (e.g. that many non-attendees were businessmen) might not be applicable to wider populations, whereas more general insights could well be true (e.g. that factors related to occupation may be relevant to attendance for surgery). In this way, theories can be developed with qualitative research, by induction; using quantitative research methods, the same theories may then be tested, deductively.[4]

Qualitative research methods are numerous and well described.[4–6] The theoretical basis of qualitative research is as sophisticated as that of quantitative research, but many of the techniques are relatively accessible and have obvious relevance to our specialty. In qualitative research, 'observation' is used to detail the lives and conversations of people – an approach which has resonance with the observational methods that underpin much of our knowledge of disease processes. The researcher may choose from a spectrum of observational styles. These range from watching overtly (recognized as an observer of the group, with no participation), to watching covertly (recognized only as a participant in the group, not as an observer).

Interviews and questionnaires range from the structured, with ordered lists of standardized questions, to the in-depth, with open-ended discussions, the direction of which is substantially determined by the interviewee. The aim of the open-ended discussion is to elucidate the subject's own (often unpredictable) framework of meaning and to avoid the imposition of the researcher's assumptions on the process. This may be contrasted with clinical history taking, in which the objective is to fit the facts into a predetermined category of disease. Focus groups (frequently used in advertising and politics) are a form of interview which makes use of group interaction. Group processes can help participants to explore and clarify their views interactively, and can access forms of communication (e.g. humour) more characteristic of everyday life than of one-on-one interviews. Synthesizing the data from several focus groups can provide different perspectives on the same issue – for example, those of chronic pain patients, female general practitioners, and academic specialists in relation to medical competence.[7]

Consensus methods are the 'meta-analyses' of qualitative research. Their aim is to determine the extent of agreement within a defined group concerning a particular issue – the causes of delays in the operating room, for example.[8] Consensus methods permit the inclusion of evidence from a wider range of sources than would be possible with a quantitative meta-analysis. Formal techniques are used to minimize the risk of dominance by an individual or subgroup with a possible vested interest. Anonymity, iteration and controlled feedback facilitate progression from entrenched or long-held views, and statistical measures may be used to provide more information about the average and dispersion of the group's response than a consensus statement on its own.

How does qualitative research differ from quantitative?

One of the strengths claimed for qualitative research is that its findings have 'validity' for a given individual or group of individuals.[4] In other words, qualitative methods show how people actually behave and think in everyday environments, whereas much quantitative research is carried out in highly controlled, sometimes even contrived environments, and may have little application to the 'real world' of clinical medicine. In contrast, two of the strengths claimed for quantitative methods are 'reliability' and 'objectivity'.[4 6] In fact, none of these characteristics can be assured simply on the basis of the type of research involved. There is no reason why qualitative research should not be reliable, or why quantitative research should rate poorly on validity. On the other hand, not all quantitative research is necessarily reliable or even particularly objective. For example, the use of numeric methods (visual analogue scores and PCA estimates of opioid consumption) does not necessarily diminish the subjectivity of the phenomenon under investigation (assessment of pain). Poor statistical methods have long been a widespread problem in medical research[9] – and, even if correctly calculated, distinguishing statistical from clinical significance may require (subjective) judgement.

A systematic review or meta-analysis can only be as good as the RCTs on which it is based, and there are many pitfalls in the design and conduct of an RCT. A review of 108 (predominantly quantitative) studies of pain control after thoracotomy identified only 32 that could be reliably interpreted.[10] Indeed, the 'evidence-base' for much contemporary clinical practice goes unheeded or is itself questionable. In some situations, practitioners may be unaware of new evidence, and this is one of the problems which systematic reviews attempt to address, particularly those updated regularly by organizations such as the Cochrane Collaboration. Unfortunately, differences may occur between the conclusions of individual smaller RCTs, different meta-analyses, or a given meta-analysis and a subsequent larger RCT.[11] Typically, RCTs address one specific issue whereas clinical decisions usually require a synthesis of (occasionally conflicting) information and objectives. Clinical practice is often based predominantly on personal experience (of the practitioner or his or her teachers) and, indeed, there are times when personal experience should rightly be considered no less important than science.[12]

Of course, qualitative research has as many problems as quantitative research. For example, it is particularly prone to the Hawthorne effect (or the 'effect on the behaviour of the subjects of the watcher watching') and to the risk of observer bias. When first considering qualitative research, some anaesthetists might experience understandable discouragement when confronted with some of its more arcane terminology (e.g. ethnomethodology)[5] and some of its philosophical links (e.g. to feminism, positivism and even Marxism).[5] Nevertheless, qualitative research is as capable as quantitative of providing insights into, information about, and understanding of our patients, our practices and the world in which we live. There is clearly a continuum between qualitative and quantitative research, and it seems self-evident that the two techniques complement each other. Qualitative research is often an essential preliminary to quantitative work. For example, it would be important to understand patients' definition of such words as 'anxious', 'worried' and 'nervous' before conducting a study related to the effect of preoperative information on 'anaesthetic risk'. Qualitative research can also supplement quantitative. The term 'triangulation' describes the idea of evaluating the same issue from different perspectives, through the use of more than one research method, to increase the range of information and improve the validity of the results.[4] Thus, the same anaesthetic researchers might use a questionnaire, focus groups and galvanic skin response to assess preoperative anxiety about the risk of anaesthesia. Most importantly, qualitative research can be used to explore phenomena which quantitative methods cannot (and conversely). Promoting either approach to the exclusion of the other serves only to ensure an incomplete picture of the phenomena under investigation.

Why should anaesthetists carry out qualitative research?

If therapy is to succeed, understanding the issues related to practitioners' actual behaviour (as opposed to descriptions of 'best practice'),[13] [14] and to patients' expectations[15] and compliance are as important as the quantitative data concerning the efficacy of various techniques and treatments. In particular, we have neglected to ask those who are most concerned with treatment – our patients – about their views, or we have done so only in limited and highly structured ways.[15] As an example, in a recent set of (otherwise very useful) guidelines published by The Royal College of Anaesthetists, the section entitled 'Patient's Perspective' acknowledges the lack of relevant data.[2] On the other hand, reports concerning the personal experiences of patients are often highly illuminating, and provide a unique and valuable insight into the doctor–patient interface.[16] [17] A lack of understanding of the patient's perspective may be particularly problematic in relation to the provision of informed consent. There has been a shift of legal opinion away from the Bolam test, which placed considerable weight on what the 'reasonable doctor' thought patients 'ought' to be told, towards a test based on what the 'reasonable patient' would 'want to know' in the circumstances.[15] [18] This presupposes considerable insight into the mind of the person giving consent. The amount of information given in any situation continues to be a matter of opinion, but the opinion at stake is that of the patient – something omitted altogether from most hierarchies of the evidential basis for practice.

Although further improvements to anaesthetic agents and monitors may be around the corner, we could do better with those already to hand. Achieving safety in anaesthesia depends as much on the behaviour and environment of anaesthetists as on their knowledge, drugs or equipment. In this we are no different from other medical specialties. The extent of the problem of accidents and negligence in healthcare[19] raises questions about the culture of hospitals, the motivations of practitioners, the interactions of different health professionals with each other and their patients, and the factors which predispose to hazardous behaviour. Tragedies continue to occur in anaesthesia, through failing to check the machine before starting a list;[20] tolerating inadequate assistance during anaesthesia;[21] working when fatigued;[22] giving the wrong drug;[14] leaving anaesthetized patients unattended;[23] and failing to provide adequate supervision to junior staff.[24] Progress could be made towards a better understanding of these important issues with relatively concrete and straightforward qualitative methods.

Important caveats

There must be a venue for publication of good qualitative studies in anaesthesia. Unless there is a home within the reputable anaesthetic literature for relevant qualitative research, such work will be published elsewhere or simply not performed, and it will be lost to practising clinical anaesthetists. Of 261 articles concerned with humans published between July 1998 and June 1999 in the *British Journal of Anaesthesia*, 207 investigations were primarily prospective trials (92 of which were controlled and randomized), 25 were reviews (three of which were systematic, including two with meta-analyses), 26 were case reports and three were surveys. One of the surveys was the only article that referred explicitly to qualitative data (as well as quantitative), and to a qualitative method of data analysis.[25] The outstanding feature of qualitative research published in this journal is its paucity.

The value of research must be judged not by its category but rather by the interest, meaningfulness and importance of its results, and by the appropriateness and rigour of the methods used. Nevertheless, if anaesthetists are to embrace qualitative research, the high standards we have come to expect in quantitative studies must be maintained. Qualitative studies need to be evaluated just as critically as quantitative. Criteria for this purpose have been published and, in essence, are not dissimilar to those pertaining to quantitative research.[26] [27] Poorly conceived or executed research must be rejected, but qualitative research should not be discarded because the reviewers are biased or unfamiliar with it. It follows that journal editors will need reviewers who are familiar with, and able to assess, qualitative methods.

In conclusion, more published reports of peer-reviewed qualitative studies are needed in the anaesthetic literature if anaesthetists are to develop a full understanding of the nature of anaesthetic practice, and to address important questions about the behaviour of themselves and their patients. We should support research which addresses the beliefs, perceptions and motivations which influence how we and our patients participate with each other, as well as research which quantifies the impact of our interventions. Healthcare ought to be appropriate and desired as well as effective. In achieving these objectives, the evidence from qualitative research is no less important than that from quantitative studies.

A. F. Merry
Department of Anaesthesia
Green Lane Hospital, and
Section of Anaesthetics
University of Auckland
Auckland
New Zealand

J. M. Davies
J. R. Maltby
Department of Anaesthesia
Foothills Medical Centre
University of Calgary
Calgary
Canada

References

1 Douketis JP, Feightner JW, Attia J, Feldman WF. Periodic health examination, 1999 update: 1. Detection, prevention and treatment of obesity. Appendix 1: levels of evidence and grades of recommendations of the Canadian Task Force on preventive health care. *Can Med Assoc J* 1999; **160**: 513–25
2 The Royal College of Anaesthetists. *Guidelines for the Use of Non-steroidal Anti-inflammatory Drugs in the Perioperative Period.* London: The College, 1998
3 American Society of Anesthesiologists Task Force on Preoperative Fasting. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures. *Anesthesiology* 1999; **90**: 896–905
4 Mays N, Pope C (eds) *Qualitative Research in Health Care* London. BMJ Publishing Group, 1996
5 Denzin NK, Lincoln YS. *Handbook of Qualitative Research* Thousand Oaks (CA): Sage Publications, 1994
6 Morse JM, Field PA *Qualitative Research Methods for Health Professionals*, 2nd edn. Thousand Oaks (CA): Sage Publications, 1995
7 Large RG. *Maintaining Doctors' Competence.* Wellington: Medical Council of New Zealand, 1997
8 Eagle CJ, Davies JM. Current models of 'quality' – an introduction for anaesthetists. *Can J Anaesth* 1993; **40**: 851–62
9 Altman DG. Statistics in medical journals: developments in the 1980s. *Stat Med* 1991; **10**: 1897–913
10 Kavanagh BP, Katz J, Sandler AN. Pain control after thoracic surgery: a review of current techniques. *Anesthesiology* 1994; **81**: 737–59
11 White PF, Watcha MF. Has the use of meta-analysis enhanced our understanding of therapies for postoperative nausea and vomiting? *Anesth Analg* 1999; **88**: 1200–2
12 Jewell D. Use of personal experience should be legitimised. *BMJ* 1999; **319**: 296
13 Galletly DC, Rowe WL, Henderson RS. The anaesthetic record: a confidential survey on data omission or modification. *Anaesth Intens Care* 1991; **19**: 74–8
14 Merry AF, Peck DJ. Anaesthetists, errors in drug administration and the law. *NZ Med J* 1995; **108**: 185–7
15 Garden AL, Merry AF, Holland RL, Petrie KJ. Anaesthesia information – what patients want to know. *Anaesth Intens Care* 1996; **24**: 594–8
16 Simini B. Patients' perceptions of intensive care. *Lancet* 1999; **354**: 571–2
17 Cobcroft MD, Forsdick C. Awareness under anaesthesia: the patients' point of view. *Anaesth Intens Care* 1993; **21**: 837–43
18 Davies JM, Robson R. The view from North America and some comments on 'Down Under'. *Br J Anaesth* 1994; **73**: 105–17
19 Berwick DM, Leape LL. Reducing errors in medicine. *BMJ* 1999; **319**: 136–7
20 Du Chateau C. Some deaths are never the end. *New Zealand Herald* 1998 Oct 3; Sect A: 15
21 Kluger MT, Bukofzer M, Bullock M. Anaesthetic assistants: their role in the development and resolution of anaesthetic incidents. *Anaesth Intens Care* 1999; **27**: 269–74
22 Savill R. Tired doctor cleared over patient's death. *The Daily Telegraph* 1995; May 20: 3
23 Williams LS. Anesthetist receives jail sentence after patient left in vegetative state *Can Med Assoc J* 1995; **153**: 619–20
24 Dyer C. Doctors cleared of manslaughter. *Br Med J* 1999; **318**: 148
25 Scriven PM. Evaluation of flexible (part-time) training in anaesthesia. *Br J Anaesth* 1998; **81**: 268–70
26 Rowan M, Huston P. Qualitative research articles: information for authors and peer reviewers. *Can Med Assoc J* 1997; **157**: 1442–6
27 Popay J, Williams G. Qualitative research and evidence-based healthcare. *J Roy Soc Med* 1998, **91** (suppl 35): 32–7

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CLINICAL INVESTIGATIONS

Reducing stress responses in the pre-bypass phase of open heart surgery in infants and young children: a comparison of different fentanyl doses† §

H. P. Duncan, A. Cloote, P. M. Weir, I. Jenkins, P. J. Murphy, A. K. Pawade, C. A. Rogers[1] and A. R. Wolf*

Royal Hospital for Sick Children, St Michael's Hill, Bristol BS2 8BJ, UK.
[1]RDSU, Southmead Hospital, Bristol, UK.
**Corresponding author: e-mail: awolfbch@aol.com*

High-dose opioids are advocated for paediatric cardiac surgery to suppress stress responses but they can produce unwanted side effects. There are no data on the dose-dependent effects of opioids on the stress response on which to base rational opioid administration. We conducted a dose ranging study on 40 children less than 4 yr undergoing elective open heart surgery using one of five fentanyl doses: 2, 25, 50, 100 or 150 μg kg^{-1} before surgery. The standardized anaesthetic also included pancuronium and isoflurane. Blood samples were taken at induction, before incision, after sternotomy, immediately before, and at the end of cardiopulmonary bypass. Patients in the 2 μg kg^{-1} group had significant rises in pre-bypass glucose ($P<0.01$), pre- and post-bypass cortisol ($P<0.01$), and pre- and post-bypass norepinephrine ($P<0.01$). No significant rise occurred in glucose, cortisol and catecholamines in any of the higher dosage groups. Patients in the 2 μg kg^{-1} group had significantly higher mean systolic blood pressure ($P<0.02$) and heart rate ($P<0.04$). A balanced anaesthetic containing fentanyl 25–50 μg kg^{-1} is sufficient to obtund haemodynamic and stress responses to the pre-bypass phase of surgery. Higher doses of fentanyl (100 and 150 μg kg^{-1}) offer little advantage over 50 μg kg^{-1}, and can necessitate intervention to prevent hypotension.

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Inadequate analgesia in infants undergoing open heart surgery is associated with a substantial hormonal and metabolic response which has been claimed to impair post-operative recovery and survival.[1–3] In addition, low-dose opioid techniques fail to prevent unwanted reflexes such as disturbances of cardiac rhythm at sternotomy,[4] and undesirable pulmonary and systemic vascular responses to stimulation.[5] In contrast, high doses of opioids introduce new side effects. Preliminary studies on infants undergoing cardiopulmonary bypass (CPB) using sufentanil at doses as high as 40 μg kg^{-1} were associated with oversedation and delayed extubation.[6] Moreover, high-dose fentanyl causes cardiovascular instability and dose-dependent impairment of T-cell function.[4 7 8]

In clinical practice, doses of fentanyl used in the pre-bypass phase of surgery vary between 2 and 200 μg kg^{-1}, based more on personal preference than available dose-dependent data. Yaster has demonstrated that neonates undergoing major non-bypass surgery have significant cardiovascular responses to surgery with doses less than fentanyl 10 μg kg^{-1}, but that an initial dose of 12.5 μg kg^{-1} provides adequate haemodynamic stability to surgery for 120 min.[9] Anand and Hickey's study on infants undergoing CPB using large doses of sufentanil from 5 to 15 μg kg^{-1} demonstrated suppression of the stress response in the pre-bypass phase of surgery.[3] This sufentanil dose is approximately equivalent to fentanyl 150 μg kg^{-1}.[10 11] On the basis

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of these data, and an accompanying editorial, high-dose opioid techniques have become popular in infants undergoing major surgery.[12] However, there are no data on what constitutes an effective high-dose fentanyl regimen in the pre-bypass phase of surgery. In order to elucidate a more rational approach, we have therefore conducted a prospective randomized trial to determine the effect of different doses of fentanyl on the suppression of hormonal, metabolic and cardiovascular responses in the pre-bypass phase of cardiac surgery.

Materials and methods

After local ethical approval (United Bristol Health Care Ethical Committee) and informed, written parental consent, we studied 40 infants and small children aged under 4 yr undergoing elective open cardiac surgery. The patients were allocated to one of five doses of fentanyl: 2, 25, 50, 100 and 150 μg kg^{-1} using individual, closed envelope randomization. The researcher and anaesthetist were aware of the dose allocated, but anaesthesia was performed in a standardized fashion to eliminate bias. Patients were excluded if they had been stressed before the operation (major cardiopulmonary collapse or ventilated before the operation), or had received opioids or corticosteroids in the period before the operation.

Patients over 4 months received either diazepam or midazolam 0.5 mg kg^{-1} orally for premedication. After gaseous induction of anaesthesia with sevoflurane, a peripheral venous cannula was inserted from which a baseline venous blood sample (2.5 ml) was taken for measurement of whole blood glucose, plasma catecholamines and cortisol. Following the baseline blood sample, fentanyl 2 μg kg^{-1} was given as a bolus with pancuronium 0.1 mg kg^{-1} prior to intubation and ventilation. An additional infusion of fentanyl was then given over 30 min to achieve the total allocated dose prior to the start of surgery. Central venous, arterial and urinary catheters were inserted, and haemodynamic parameters were recorded throughout at 5-min intervals, initially non-invasively and later via the indwelling arterial catheter. Heart rate, central venous pressure and oxygen saturation by pulse oximetry were monitored and recorded routinely as well as at the time of each blood sample.

Feeds were withheld for 3 h before the operation. Dextrose infusions were not used pre- or intraoperatively. Hartmann's solution was not used routinely during the pre-bypass period, but fluid administration was allowed if the mean blood pressure dropped to below 40 mm Hg. Transient falls in blood pressure due to surgical manipulations were not treated with fluids or drugs. Gentamicin 4 mg kg^{-1} and flucloxacillin 30 mg kg^{-1} were given routinely. Anaesthesia was maintained with air, oxygen and low-dose isoflurane (0.2–0.4%). Phenylephrine was used for episodes of systemic hypoxia and hypotension in patients with Tetralogy of Fallot, and isoflurane up to 2% was allowed briefly in response to an episode of hypertension. Inotropic support was not used unless systemic hypotension unresponsive to a fluid bolus occurred. In these circumstances, a dopamine infusion of 5 μg kg^{-1} min^{-1} was commenced and this was recorded. Heparin 3 mg kg^{-1} was administered prior to the pre-bypass blood sample. Morphine 0.5 mg kg^{-1} and dexamethasone 0.5 mg kg^{-1} were given into the CPB circuit immediately after the initiation of CBP. The cardiotomy prime consisted of fresh frozen plasma, human albumin 4.5% solution, blood and Plasmalyte 148. The prime solution was tested to ensure that the glucose concentration was in the physiological range, and additional glucose added if necessary before commencing cardiopulmonary bypass.

Further blood samples were taken from the arterial catheter before surgery, 5 min after sternotomy and directly before initiation of CPB. A final sample was taken from the cardiotomy reservoir before separation from CPB. Whole blood glucose was measured using a glucose oxidase method (One touch®, coefficient of variation <4.0% in measured range). Plasma cortisol samples were measured by chemiluminescence (ACS: 180) with a sensitivity of 5.5 nmol litre^{-1} and inter-assay variability of 6.4% (range 4.5–7.6%). Blood samples for measurement of catecholamines were cooled immediately on ice, and the plasma separated and stored at –70°C until assay. After extraction (Chromsystems extraction kit), norepinephrine and epinephrine were measured using an HPLC method. The recovery on extraction was measured as 72% for norepinephrine and 70% for epinephrine. The intra-assay and inter-assay precision at normal levels was measured at 5.8% and 6.1% for norepinephrine, and 5.4% and 6.1% for epinephrine.

Following surgery, patients were cared for in the paediatric intensive care unit (PICU). Data on clinical outcome were collected at the bedside as well as following a formal review of medical and nursing records following discharge from hospital or death. The time taken till extubation and the length of stay in intensive care were noted for each child. Complications including postoperative infection (septicaemia, chest infection, intravenous line infection and wound infection) were documented for the period up to discharge from hospital.

Statistical analysis

To establish the sample size, we selected plasma cortisol and blood glucose[13] as relevant clinical variables, and an effect size of 0.6 was considered to represent a clinically relevant difference between the means. From a standard nomogram, a sample size of eight patients per group was determined to be sufficient to give the trial 80% power to detect a difference at the 5% significance level.[14]

A series of mixed models were fitted in order to examine the effect of the fentanyl dose on the haemodynamic and biochemical parameters measured. The data followed a repeated-measures design with the parameters being measured before randomization and at four stages (biochemical data) or five stages (haemodynamic data) during the opera-

Table 1 Physical characteristics. *Values given as median (range) †Values given as mean (SD) min

Fentanyl dose	2 μg kg^{-1}	25 μg kg^{-1}	50 μg kg^{-1}	100 μg kg^{-1}	150 μg kg^{-1}
Age* (months)	13.5 (2–44)	14.5 (0.3–31)	14.5 (4–33)	13 (2–45)	11 (0.3–24)
Weight* (kg)	8.2 (4–13.5)	7.7 (3.2–11.8)	8.5 (4.3–12.8)	9.5 (4.7–13.1)	8.7 (3.7–10.9)
Surgery					
Aortic root	1	1	0	2	
Fallot's type	3	1	1	3	2
ASD, VSD, AVSD	4	3	5	2	3
Arterial switch	0	1	0		1
Cavopulmonary shunt	2	2	1	2	
CPB time†	59.4 (19.7)	68.6 (36.7)	44.6 (20.4)	58.8 (17.3)	58.1 (26.7)

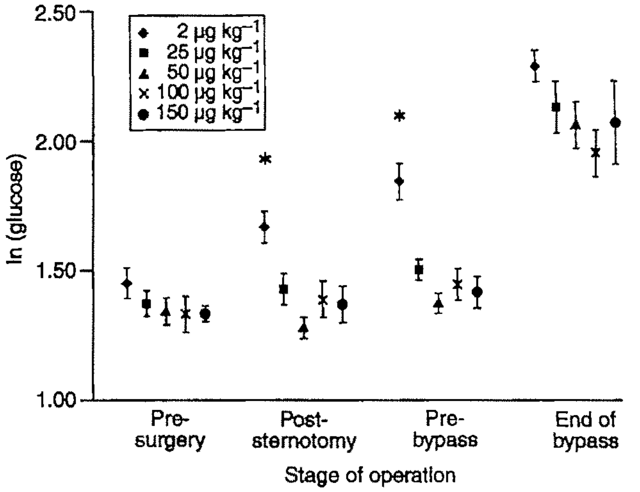

Fig 1 Mean (SE) ln(glucose) versus stage of surgery for each dose of fentanyl The values for the post-sternotomy and pre-bypass measurements were significantly different (*$P<0.01$), with the mean ln(glucose) for the 2 μg kg^{-1} group being higher than the other groups (ln = natural logarithm).

tion. A mixed model was chosen to allow the correlation between readings taken from one child to be modelled explicitly in the analysis. A variety of correlation structures were examined, and the structure giving the highest values for the Akaike's information criterion[15] and/or Schwarz's Bayesian criterion was selected in each case. These criterion take into account both statistical goodness of fit of a model and the number of parameters that need to be estimated to achieve this degree of fit, by imposing a penalty for increasing the number of parameters. The preferred model is the one with the lowest number of parameters that still provides an adequate fit to the data. For the biochemical measurements, it was necessary to transform the data to a logarithmic scale (ln) in order to satisfy the assumptions of the model. The results for the biochemical data are therefore presented as the natural logarithm, with the original data presented as an appendix (Appendices 1–4). All analyses included adjustment for the baseline reading. Analyses for cortisol and pulse were adjusted for age. Interaction between fentanyl dose and the stage of operation was assessed. Any interactions found to be statistically significant at the 5% level were retained. For each fentanyl dose, the mean response and standard error were estimated from the model using the least-squares method. Where interactions were found between dose and stage of operation, the mean response was estimated separately for each stage of the operation. The Bonferroni correction for multiple comparisons was applied when comparing individual dosing levels. Residual plots were used to assess the models adequacy. A small number of outlying observations were found and the models fitted with and without these readings in order to assess their impact on the model. The results are reported excluding these outliers because although the conclusions remain unchanged, the estimates of means can be influenced by outliers. The log rank test was used to assess the effect of fentanyl dose on the child's length of stay in PICU and on the time the child was ventilated. Patients who died in PICU or whilst receiving ventilatory support were censored at death. All analyses were performed using SAS.[16]

Results

The results are reported on 40 infants and young children. Patients in each of the five groups were similar in age, weight and type of surgical procedure and length of CPB time (Table 1).

All baseline measurements were similar across the five groups. The biochemical data are expressed as the natural logarithm (ln) according to the statistical model, and the untransformed data are presented in Appendices 1–4. The mean ln(glucose) differed significantly between the groups ($P<0.01$) in the post-sternotomy and pre-bypass stages. At both stages, the mean ln(glucose) was significantly higher for the 2 μg kg^{-1} group than the other doses which showed similar responses (Fig. 1). There was no significant difference in the mean ln(glucose) between any of the other groups in the pre-bypass phase. All groups showed a rise in blood glucose at the end of bypass, but there was no difference between the groups.

The ln(cortisol) measurements showed a similar response. There was a significant difference between the groups pre-bypass and at the end of CPB ($P<0.01$); the mean ln(cortisol) for the 2 μg kg^{-1} group was significantly higher than for the other groups, which responded similarly (Fig. 2).

The mean ln(norepinephrine) was significantly higher in

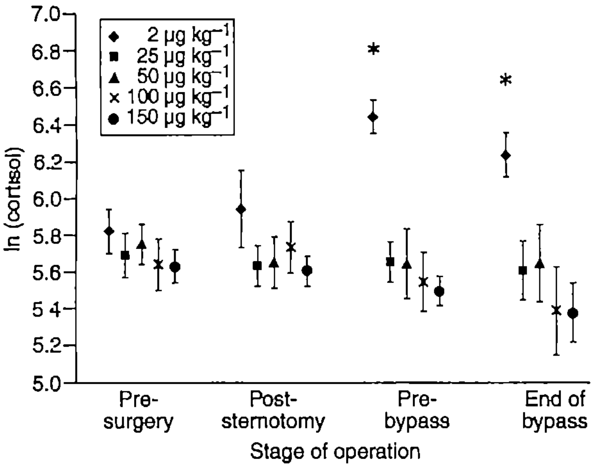

Fig 2 Mean (SE) ln(cortisol) versus stage of surgery for each dose of fentanyl. The values for the pre-bypass and end of bypass measurements were significantly different (*$P<0.01$) with the mean ln(cortisol) in the 2 μg kg^{-1} group being higher than other groups (ln=natural logarithm).

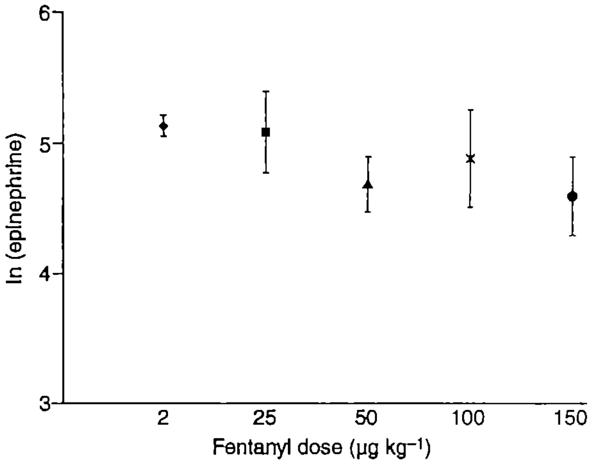

Fig 4 Mean (SE) ln(epinephrine) versus fentanyl dose. No significant difference between groups (ln = natural logarithm).

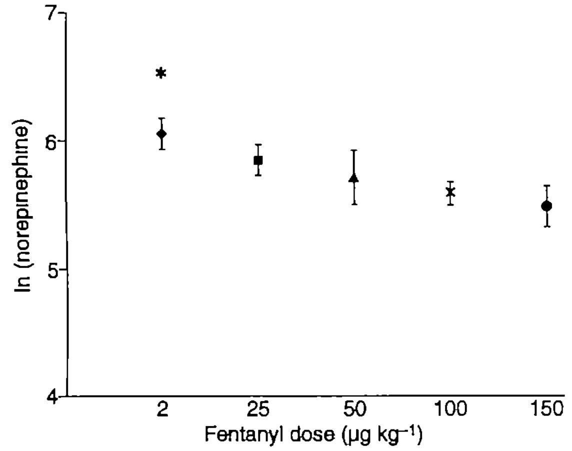

Fig 3 Mean (SE) ln(norepinephrine) versus fentanyl dose. The mean for the 2 μg kg^{-1} group was significantly higher than the mean for the 150 μg kg^{-1} group (*$P<0.01$) (ln=natural logarithm)

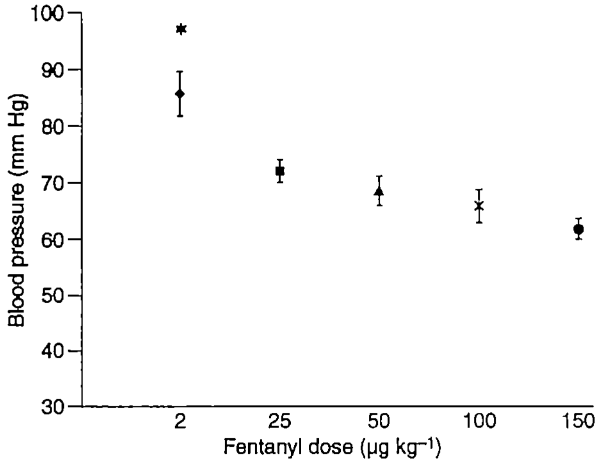

Fig 5 Mean (SE) systolic blood pressure versus dose of fentanyl. The mean systolic blood pressure in the 2 μg kg^{-1} group was significantly higher (*$P<0.02$) for all comparisons.

the 2 μg kg^{-1} group compared to the 150 μg kg^{-1} group which did not change with the stage of surgery. No other differences between the groups were found (Fig. 3). The epinephrine measures showed wide variability and no significant differences were detected (Fig. 4).

The mean systolic blood pressure for the 2 μg kg^{-1} dose was significantly higher than all the other doses ($P < 0.02$ for all comparisons). There was no interaction between dose and time of operation. The groups receiving 100 and 150 μg kg^{-1} had lower mean systolic blood pressure than the 25 and 50 μg kg^{-1} groups, but the differences failed to reach statistical significance. However, two out of eight children in each group receiving 100 and 150 μg kg^{-1} required fluid boluses to maintain adequate blood pressure prior to surgery (Table 2, Fig. 5).

The mean heart rate was significantly higher in the 2 μg kg^{-1} group ($P<0.04$ for all comparisons) and there was no difference in the heart rates of children receiving higher doses (Table 2, Fig. 6).

There were no significant differences between the five groups in relation to time to extubation, time spent in PICU, and the incidence of infection or postoperative complications. There were two deaths in the study group. One patient in the 150 μg kg^{-1} group, having undergone a bidirectional Glen shunt, died suddenly at 24 h after the operation. The second patient, allocated to receive fentanyl 25 μg kg^{-1}, had Down's syndrome and died 6 weeks after a complete atrioventricular septal defect repair. Pulmonary hypertension, pericardial effusion and multiple thrombi in several major blood vessels complicated her course.

Discussion

Stress responses to paediatric cardiac surgery are dependent not only on anaesthetic technique but also on patient age, type of surgery, management of cardiopulmonary bypass

Table 2 Haemodynamic data expressed as mean (SE). *$P<0.05$

Dose	2 µg kg^{-1}	25 µg kg^{-1}	50 µg kg^{-1}	100 µg kg^{-1}	150 µg kg^{-1}
Systolic blood pressure (mm Hg)	85.6 (3.09)*	71.1 (1.97)	68.0 (2.94)	65.0 (2.57)	61.0 (1.66)
Pulse rate (min^{-1})	136.8 (2.02)*	121.2 (3.00)	122.3 (4.15)	115.8 (3.55)	118.5 (2.57)

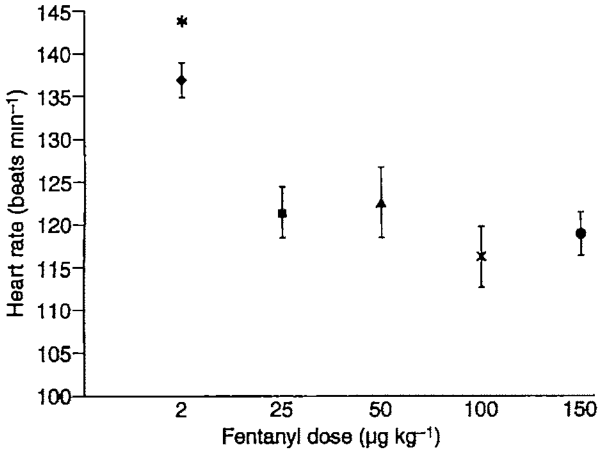

Fig 6 Mean (SE) heart rate versus dose of fentanyl The group receiving 2 µg kg^{-1} demonstrates a significantly higher heart rate than other groups (*$P<0.04$) for all comparisons.

and whether circulatory arrest is used as part of the bypass technique. This study was designed to study the effects of different opioid doses on the hormonal/metabolic and cardiovascular responses to the pre-bypass phase of cardiac surgery in a population of infants and young children. Our results indicate, not surprisingly, that fentanyl 2 µg kg^{-1} given as part of a low-dose isoflurane anaesthetic does not suppress the pre-bypass responses. However, in this study population, a dose of fentanyl 25 µg kg^{-1} given after induction of anaesthesia and before surgery suppressed glucose, cortisol, catecholamine and haemodynamic responses as effectively as fentanyl 150 µg kg^{-1} in the pre-bypass phase of cardiac surgery. Moreover, fentanyl 25 µg kg^{-1} and 50 µg kg^{-1} provided the least cardiovascular disturbance during the pre-bypass phase.

Few previous studies have attempted to relate the dose-dependent effects of opioids on suppression of adverse responses to either cardiac or non-cardiac surgery, and the results are difficult to interpret collectively due to wide differences in the populations studied and the different opioid doses used. In evaluating the effects of different opioid doses on the stress response, it is important to distinguish the pre-bypass phase of surgery from the bypass and post-bypass phases. During the pre-bypass phase, the nociceptive input from somatic and visceral nerves represents the main stimulus to the neuroendocrine responses, while on bypass the effects of hypothermia, hypotension and the inflammatory responses become major stimulating factors. Fentanyl is an appropriate drug for the pre-bypass phase of cardiac surgery due to its rapid onset and relative cardiovascular stability, but it is not an ideal drug for maintenance of anaesthesia and stress reduction during cardiopulmonary bypass. The plasma concentration of fentanyl falls rapidly on bypass due to dilutional effects as well as adhesion of the drug to the surface of silicone membrane oxygenators.[17,18] We believe that for an effective understanding of stress responses and their control during cardiac surgery, it is necessary to address the pre-bypass, bypass and post-bypass phases separately. The results of this study pertain specifically to the dose-dependent effects of fentanyl on the stress response in the pre-bypass phase of open cardiac surgery. We chose to use morphine during bypass because its plasma and biophase concentrations are likely to be better preserved during bypass than more lipid-soluble drugs.

The only comprehensive evaluation of stress responses to cardiac surgery in paediatrics was performed in a neonatal population having complex surgical repairs using hypothermic circulatory arrest.[3,19] In the control group, an initial dose of morphine 0.1–0.2 mg kg^{-1} was given with a mean intraoperative dose of 0.35 mg kg^{-1}. This is lower than the opioid doses used in our control group (fentanyl 2 µg kg^{-1} initially with morphine 0.5 mg kg^{-1} during cardiopulmonary bypass). Anand's high-dose opioid group consisted of an initial dose of sufentanil 5–15 µg kg^{-1} with a mean dose during surgery of 37 µg kg^{-1}.[2] These values are approximately equivalent to an initial fentanyl dose of 50–100 µg kg^{-1} and a total intraoperative fentanyl dose of 370 µg kg^{-1},[11,20] clearly much higher than used in any other study. High-dose sufentanil suppressed the adrenocortical and beta endorphine responses not only in the pre-bypass period but also for up to 24 h post-bypass. However, while there was no rise in catecholamines in the pre-bypass phase, high-dose sufentanil was unable to completely suppress the adrenomedullary and sympathetic responses to cardiopulmonary bypass and hypothermic arrest. Glucose concentrations rose significantly even in the sufentanil group, but this may have merely reflected the administration of intravenous glucose before bypass and the composition of the priming solution used for the bypass pump. A more recent paediatric study evaluated neuroendocrine responses to cardiac surgery after an induction dose of fentanyl 25 µg kg^{-1} and a total pre-bypass dose of fentanyl 100 µg kg^{-1}.[21] Two groups were compared, namely infants under 1 yr with an older more heterogeneous paediatric group. The results showed that 100 µg kg^{-1} was sufficient to prevent the rise in catecholamines during surgery and bypass even in the younger age group. However, aortic occlusion during bypass did cause a significant rise in neuropeptide Y (a sensitive measure of sympathetic stimulation) and this was greater in the older age group. Doses as low as fentanyl 10 μg kg^{-1} still appear to be relatively effective in suppression of the stress responses for non-cardiac surgical procedures of short duration, both in preterm neonates and older children.[2 22] However, infants undergoing cardiac or major non-cardiac surgery using doses of fentanyl below 10 μg kg^{-1} (or an equivalent) demonstrate significant neurohumoral responses[3 17 23 24] despite having haemodynamic stability during surgery and excellent analgesia in the immediate postoperative period.[23 24] These data therefore support the findings from the present study that doses of fentanyl 25–50 μg kg^{-1} are sufficient to block neuroendocrine responses in the pre-bypass phase.

High-dose opioid analgesia is also used to provide haemodynamic stability during surgery, but the effective dose is dependent on age, the intensity of the stimulus and the presence of additional anaesthetic agents. Early studies on fentanyl in the cardiac infant indicated that 25 μg kg^{-1} had minimal effects on heart rate, cardiac index, and pulmonary or systemic vascular resistance,[5] and that 25–30 μg kg^{-1} was sufficient to obtund pulmonary and systemic vascular responses to suctioning and intubation.[25 26] However, while doses as low as 12.5 μg kg^{-1} have been shown to provide suppression of haemodynamic responses to major thoracic and abdominal surgery in the neonate,[9] studies of fentanyl as the sole anaesthetic agent for infant cardiac surgery have reported that doses as high as 75 μg kg^{-1} still do not appear to be effective at reliable suppression of the haemodynamic response to surgical incision and sternotomy.[11] Moreover, it has been suggested that doses less than 50 μg kg^{-1} may be associated with a higher incidence of ventricular fibrillation during the pre-bypass phase in neonates undergoing surgery for hypoplastic left heart syndrome.[4] All the patients in our present study received low-dose isoflurane anaesthesia in addition to their assigned dose of fentanyl. The combination of fentanyl with an inhaled anaesthetic agent provides better suppression of cardiovascular responses to surgery than fentanyl alone.[26] This may explain the difference between previous studies using fentanyl as a sole anaesthetic agent[11 26] and the findings from this study which show that fentanyl 25–50 μg kg^{-1} combined with low-dose isoflurane anaesthesia can reliably suppress haemodynamic responses to surgical incision and sternotomy. Our choice of fentanyl 2 μg kg^{-1} and 150 μg kg^{-1} represented an approximate equivalent of the lowest and highest doses of opioids used in Anand's original study of neonates undergoing cardiac surgery.[3 6] Fentanyl 25 μg kg^{-1} was chosen as the second lowest dose because while it was more likely to give haemodynamic stability than 2 μg kg^{-1};[25 26] some studies suggest that it still remained ineffective in suppressing undesirable responses.[4 11] A complicating factor that can make comparison of this study with others difficult to interpret is the time taken from induction of anaesthesia (IA) to the start of cardiopulmonary bypass. Fentanyl rapidly redistributes into peripheral stores after single administration, and a long IA to CPB time allows more time for the biophase concentration to fall. Therefore, institutions that have relatively long IA to CPB times are likely to require more fentanyl in order to maintain suppression of hormonal and cardiovascular responses to surgery due to redistribution of the drug out of the brain. The current IA to CPB time in our institution ranges from 35 to 60 min for 'non-redo' surgery, and our results need to be interpreted within this context.

High-dose opioid techniques remain popular for paediatric cardiac surgery due to the belief that they are beneficial to postoperative recovery.[12] However, a case should be made to use the minimum effective dose rather than a dose that is well in excess of that required. High-dose opioids can delay extubation and recovery of the patient due to prolonged ventilatory depression and oversedation. This is particularly noticeable for less complex surgery when the period of cardiopulmonary bypass is brief and there is less time for sequestration of fentanyl to the oxygenator in the bypass circuit. There is also increasing evidence of dose-dependent effects of opioids on the immune system[27] Both fentanyl and morphine suppress natural killer cell cytotoxicity in a dose-dependent fashion,[7 28] and morphine has been shown to decrease the proliferation of stimulated human lymphocytes and the production of interferon α and interferon β.[29] Given the evidence that chronic opioid exposure is associated with marked immunosuppression in both animals and humans,[7 30] and that postoperative cardiac children on intensive care have a high incidence of postoperative infection, it would seem logical to avoid excessive opioids. An alternative would be to consider the use of epidural local anaesthetic techniques that can suppress stress responses without affecting immune function.[23 31]

The sample group for this study were heterogeneous both for age and operation type, but this facet of the study design was fully considered. The intended operation was to be largely irrelevant because this was a pre-bypass study measuring responses to a single procedure (sternotomy and cannulation) with the same surgeon carrying out all the procedures. Moreover, the relevance of stress response data derived from neonates undergoing cardiac surgery using deep hypothermic arrest to an older population group is questionable.[3 19] It has previously been accepted that neonates have more extreme but short-lived stress responses to surgical stimulus than the older child and adult,[32] but recent data investigating catecholamine and neuropeptide Y responses during and after aortic occlusion on cardiopulmonary bypass have questioned this belief.[21] An inclusion criterion for our study was that the patients were not stressed prior to surgery, but despite this there was a large variation in all the norepinephrine and epinephrine concentrations. Both researcher and anaesthetist were aware of the group assignment, but we considered that this would not bias data collection because the anaesthetic technique was carried out in a standardized fashion according to the protocol.

In particular, isoflurane was kept at a fixed background concentration other than to respond to a surge in blood pressure, and intravenous fluids were only given for persistent hypotension unrelated to surgical manipulation of the great vessels.

As with previous studies in non-cardiac surgery, the whole blood glucose appears to be the most useful summary measure of stress response during the pre-bypass phase, provided the infant is not receiving exogenous glucose at the time of measurement.[23 24] Glucose homeostasis is tightly controlled, and the rise in glucose during surgery is dramatic if inadequate opioid analgesia has been administered. Whole blood glucose can be measured easily during surgery, and an excessive response identified and treated almost immediately. This individualized approach with real time feedback of the stress response may be far better than either using an excessive dose in the hope of ablation of the stress response, or using a minimal opioid dosage based on a heterogeneous population.

The current practice in our institution is for the priming solution of the cardiopulmonary bypass pump to contain a glucose concentration within the normal physiological range. However, there was a substantial rise in whole blood glucose at the end of bypass irrespective of group allocation. Clearly, a high-dose opioid strategy in the pre-bypass phase was unable to prevent this response and further research is required in this area. This failure to maintain normal glucose concentration may be potentially harmful to the brain, particularly if low flow or circulatory arrest is required.[33] The rise in glucose in all groups was not matched by a similar rise in plasma cortisol. This independent rise in glucose has been previously described and ascribed to reduction of insulin production during moderate hypothermia and a failure to utilize glucose peripherally.[34]

Acknowledgements

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References

1. Anand KJS, Hickey PR Pain and its effects on the human neonate and fetus. *NEJM* 1987; **317**: 1321–9
2. Anand KJS, Sippell WG, Aynsley-Green A. Randomised trial of anaesthesia in preterm babies undergoing surgery: effect on the stress response. *Lancet* 1987; **1**: 243–7
3. Anand KJS, Hickey PR. Halothane-morphine compared with high-dose sufentanil for anaesthesia and postoperative analgesia in neonatal cardiac surgery. *NEJM* 1992; **326**: 1–9
4. Hickey PR, Hansen DD. High-dose fentanyl reduces intra-operative ventricular fibrillation in neonates with hypoplastic left heart syndrome. *J Clin Anesth* 1991; **3**: 295–300
5. Hickey PR, Hansen DD, Wessel DL, *et al*. Pulmonary and systemic hemodynamic responses to fentanyl in infants. *Anesth Analg* 1985; **64**: 483–6
6. Anand KJS, Hickey PR. Randomised trial of high-dose sufentanil anaesthesia in neonates undergoing cardiac surgery: effects on the metabolic stress response. *Anesthesiology* 1987; **67**: A502
7. Beilin B, Shavit Y, Hart J, *et al*. Effects on anaesthesia based on large versus small doses of fentanyl on natural killer cell cytotoxicity in the pre-operative period. *Anesth Analg* 1996; **82**: 492–7
8. Shavit Y, Lewis JW, Terman GW, *et al*. Opioid peptides mediate the suppressive effect of stress on the natural killer cell activity. *Science* 1984; **223**: 188–90
9. Yaster M. The dose response of fentanyl in neonatal anesthesia. *Anesthesiology* 1987; **66**: 433–5
10. Hug CC, McClain DA. Opioids – pharmacology in relation to anaesthesia and post-operative pain control. In: Prys-Roberts C, Brown BR, Nunn JF, eds. *International Practice of Anaesthesia*, 1st edition. Oxford: Butterworth Heinemann, 1996; 1/18/1–21
11. Hickey PR. Hansen DD. Fentanyl- and sufentanil-oxygen-pancuronium anaesthesia for cardiac surgery in infants. *Anesth Anal* 1984; **63**: 117–24
12. Rogers MC. Do the right thing, pain relief in infants and children. *NEJM* 1992; **326**: 55–6
13. Wolf AR, Hughes D. Pain relief for infants undergoing abdominal surgery: comparison of infusions of IV morphine and extradural bupivacaine. *Br J Anaesth* 1993; **70**: 10–6
14. Day SJ, Graham DF. Sample size and power for comparing two or more treatment groups in clinical trials. *BMJ* 1989; **299**: 663–5
15. Bozdogan H. Model selection and Akaike's information criterion (AIC): the general theory and its analytical extensions. *Psychometrica* 1987; **52**: 345–70
16. SAS Institute Incorporated. *The SAS System 1996*; 6.12. Cary, NC: SAS Institute, 1996
17. Rosen D, Rosen K, Davidson B. Fentanyl uptake by the Scimed membrane oxygenator. *Journal of Cardiothoracic Anaesthesia* 1988; **2**: 619–26
18. Rosen DA, Rosen KR, Silvasi DL. *In vitro* variability in fentanyl absorption by different membrane oxygenators. *J Cardiothoracic Anaesth* 1990; **4**: 332–5
19. Anand KJS, Hansen DD, Hickey PR. Hormonal-metabolic responses in neonates undergoing cardiac surgery. *Anesthesiology* 1990; **73**: 661–70
20. Scott JC, Cooke JE, Stanski DR. Encephalographic quantitation of opioid effect: comparative pharmacodynamics of fentanyl and sufentanil. *Anesthesiology* 1991; **69**: 348–56
21. Sun LS, Du F, Schechter WS, *et al*. Plasma neuropeptide Y and catecholamines in paediatric patients undergoing cardiac operations. *J Thorac Cardiovasc Surg* 1997, **113**: 278–84
22. Koganei H, Nakaoji T, Owaki A, *et al*. Paediatric anaesthesia and stress response. *Masui-Japanese J Anesth* 1995; **44**: 553–9
23. Wolf AR, Eyres RL, Laussen PC, *et al*. Effect of epidural analgesia on the stress responses to abdominal surgery in infants. *Br J Anaesth* 1993; **70**: 654–60
24. Wolf AR, Doyle E, Thomas E. Modifying infant stress responses to major surgery: spinal vs extradural vs opioid analgesia. *Paediat Anaesth* 1998; **8**: 305–11
25. Hickey PR, Hansen DD, Wessel DL, *et al*. Blunting of stress responses in the pulmonary circulation of infants by fentanyl. *Anesth Analg* 1985; **64**: 1137–42
26. Crean P, Koren G, Goresky G, et *al*. Fentanyl-oxygen versus fentanyl-N_2O/oxygen anaesthesia in children undergoing cardiac surgery. *Can Anaesth Soc J* 1986; **33**: 36–40
27. Webster NR. Opioids and the immune system. *Br J Anaesth* 1998; **81**: 835–6
28. Yeager MP, Calacchio TA, Yu CT, et *al*. Morphine inhibits spontaneous and cytokine enhanced natural killer cell cytotoxicity in volunteers. *Anesthesiology* 1995; **83**: 500–8

29 Nair MP, Schwartz SA, Polasani R, *et al.* Immunoregulatory effects of morphine on human lymphocytes. *Clin Diagnost Lab Immunol* 1997; **4**: 127–32

30 Di Francesco P, Gaziano R, Casalinuovo IA, *et al.* Antifungal and immunoadjuvant properties of fluconazole in mice immunosupressed with morphine. *Chemotherapy* 1997; **43**: 198–203

31 Tonnesen E, Huttel MS, Christiansen NJ, *et al.* Natural killer cell activity in patients undergoing upper abdominal surgery: relationship to the stress response. *Acta Anaesthesiol Scand* 1984; **28**: 654–60

32 Anand KJS. Neonatal responses to anaesthesia and surgery. *Clin Perinat* 1990; **17**: 207–14

33 Bush GH, Steward DJ Can persistent cerebral damage be caused by hyperglycaemia? *Paediat Anaesth* 1995; **5**: 385–7

34 Jonas RA. In: Jonas RA, Elliot MJ, eds. *Metabolic Response in Cardiopulmonary Bypass in Neonates, Infants and Young Children.* Oxford: Butterworth Heinemann, 1994; 205–25

Appendix 1 Whole blood glucose concentration, absolute values (mmol litre^{-1})

	Baseline	Pre-surgery	Post-sternotomy	Pre-bypass	Post-bypass
2 $\mu g\ kg^{-1}$					
Patient 1	5.8	4.4	4.8	5.5	9.2
Patient 2	3.3	3.7	4.0	7.3	9.3
Patient 3	3.4	3.8	5.1	5.5	8.1
Patient 4	4.5	3.9	5.1	5.3	8.3
Patient 5	3.4	5.1	5.6	6.5	8.9
Patient 6	3.9	3.8	5.7	6.3	12.0
Patient 7	4.2	4.8	5.9	7.6	11.4
Patient 8	4.4	6.3	7.7	7.8	13.7
25 $\mu g\ kg^{-1}$					
Patient 1	3.4	3.8	3.9	3.9	6.1
Patient 2	3.1	3.4	4.4	3.7	6.8
Patient 3	3.4		3.5	3.1	5.0
Patient 4	4.3	5.4	5.5	12.1	13.9
Patient 5	3.9	4.3	4.1	4.1	8.3
Patient 6	4.6	3.5	3.8	5.4	11.6
Patient 7	2.2	3.2	3.5	4.1	8.6
Patient 8	3.8	3.6	3.4	4.4	6.4
50 $\mu g\ kg^{-1}$					
Patient 1	5.6	5.5	4.5	4.8	12.0
Patient 2	5.0	5.2	4.6	4.8	12.3
Patient 3	4.4	4.2	3.8	3.5	
Patient 4	3.6	3.7	2.9	3.4	
Patient 5	5.8	4.4	4.8	5.5	9.2
Patient 6	3.7	3.8	3.9	4.0	6.8
Patient 7	3.9	3.1	3.2	4.1	6.6
Patient 8	4.2	3.6	3.6	4.1	8.9
100 $\mu g\ kg^{-1}$					
Patient 1	4.0	5.9	5.8	5.1	6.6
Patient 2	3.9	3.4	4.1	5.2	7.6
Patient 3	3.4	3.1	3.0	3.7	5.4
Patient 4	3.1	2.8	2.6	2.6	6.4
Patient 5	4.6	4.2	4.5	4.8	5.8
Patient 6	3.4	4.0	4.2	4.2	5.7
Patient 7	4.1	3.7	4.1	4.6	12.4
Patient 8	2.9	3.0	3.6	3.2	5.9
150 $\mu g\ kg^{-1}$					
Patient 1	3.6	3.0	2.7	3.2	13.1
Patient 2	2.9	3.5	3.1	3.5	8.0
Patient 3	4.3	3.8	3.5	3.8	7.4
Patient 4	3.5	3.7	4.6	4.0	5.1
Patient 5	4.2	4.1	5.2	5.6	11.5
Patient 6	3.8	4.0	3.7	3.9	4.2
Patient 7	3.7	3.6	3.6	3.4	4.4
Patient 8	3.2	3.7	4.6	4.6	12.3

Appendix 2 Serum cortisol, absolute values (nmol litre^{-1})

	Baseline	Pre-surgery	Post-sternotomy	Pre-bypass	Post-bypass
2 $\mu g\ kg^{-1}$					
Patient 1	272	230	321	491	503
Patient 2	399	268	150	610	354
Patient 3	650	589	735	790	528
Patient 4	143	196	182	376	324
Patient 5	378	394	444	646	536
Patient 6	510	498	989	839	719
Patient 7	241	200	204	546	490
Patient 8	213	587	763	867	729
25 $\mu g\ kg^{-1}$					
Patient 1	301	211	192	242	125
Patient 2	336	361	281	239	236
Patient 3	393	497	457	449	234
Patient 4	322	487	449	305	378
Patient 5	265	215	244	439	558
Patient 6	318	219	212	187	318
Patient 7	772	1345	1536	1204	1140
Patient 8	517	422	398	423	414
50 $\mu g\ kg^{-1}$					
Patient 1	398	653	670	579	493
Patient 2	308	352	259	720	455
Patient 3	316	517	527	477	522
Patient 4	287	252	253	110	165
Patient 5	84	146	116	133	307
Patient 6	279	214	186	183	98
Patient 7	404	311	271	314	528
Patient 8	340	279	270	196	110
100 $\mu g\ kg^{-1}$					
Patient 1	203	525	526	380	287
Patient 2	401	350	324	318	131
Patient 3	283	257	316	286	102
Patient 4	250	518	508	410	468
Patient 5	215	221	198	103	408
Patient 6	146	113	248	248	92
Patient 7	164	110	107	98	250
Patient 8	303	249	244	210	122
150 $\mu g\ kg^{-1}$					
Patient 1	297	337	301	271	360
Patient 2	155	327	339	295	206
Patient 3	378	288	246	212	166
Patient 4	395	304	285	211	100
Patient 5	223	238	201	190	478
Patient 6	267	407	372	342	183
Patient 7	296	237	264	283	207
Patient 8	381	252	322	277	314

Appendix 3 Serum norepinephrine, absolute values (ng litre^{-1})

	Baseline	Pre-surgery	Post-sternotomy	Pre-bypass	Post-bypass
2 µg kg^{-1}					
Patient 1	312	433	489	439	352
Patient 2	1005	394	382	378	479
Patient 3	536	568	634	768	1846
Patient 4	347	319	446	331	366
Patient 5	122	140	134	185	481
Patient 6	94	91.6	102	91	2770
Patient 7	158	241	215	223	1987
Patient 8	219	195	217	212	1172
25 µg kg^{-1}					
Patient 1	398	284	496		146
Patient 2	724	730	416	132	256
Patient 3	117	156	125	122	135
Patient 4	299	329	189	477	825
Patient 5	363	228	391	436	586
Patient 6	406	380	117	296	950
Patient 7	188	143	170	178	1010
Patient 8	273	402	555	220	320
50 µg kg^{-1}					
Patient 1	45.6	362		346	336
Patient 2	705	134	364	402	876
Patient 3			185	225	212
Patient 4		185			289
Patient 5	717	160	248	277	396
Patient 6	262	558	319	385	432
Patient 7	1654	236	1181	875	856
Patient 8	122	110	74.7	87.3	177
100 µg kg^{-1}					
Patient 1	438	252	232	143	224
Patient 2	296	7700	696	2350	682
Patient 3	180	144	170		
Patient 4	72.4	71.9	155	273	757
Patient 5	1481	190	344	459	605
Patient 6	453	116	900	900	626
Patient 7	163	112	428	1390	1380
Patient 8	197	200	218	183	259
150 µg kg^{-1}					
Patient 1	560	2255	1154		
Patient 2	845	146	108	284	157
Patient 3	412	103	153	141	293
Patient 4	46	132	230	155	172
Patient 5	303	277	425	377	6382
Patient 6	236	281	288	319	944
Patient 7	808	278	147	192	195
Patient 8	83.9	95.8	279	115	627

Appendix 4 Serum epinephrine, absolute values (ng litre^{-1})

	Baseline	Pre-surgery	Post-sternotomy	Pre-bypass	Post-bypass
2 µg kg^{-1}					
Patient 1	159	280	137	104	165
Patient 2	217	94.1	214	198	284
Patient 3	108	62.9	176	132	211
Patient 4	177	146	172	189	241
Patient 5	164	77	212	171	956
Patient 6	155	56.1	82.2	86.8	560
Patient 7	104	147	85.1	52.9	901
Patient 8	160	144	103	90	243
25 µg kg^{-1}					
Patient 1	170	66	208	97	262
Patient 2	32.6	464	302	646	592
Patient 3	117	63.6	86.3	75.7	114
Patient 4	436	383	551	600	417
Patient 5	235	50.1	38.2	30.3	173
Patient 6	175	41.4	64.8	148	548
Patient 7	262	603	453	443	867
Patient 8	623	117	521	249	277
50 µg kg^{-1}					
Patient 1	91.4	154	177	40	428
Patient 2	226	136	212	193	997
Patient 3	271	132	174	114	151
Patient 4	208	109	119	63.2	286
Patient 5	256	59.1	56.3	64.6	161
Patient 6	364	127.5	87.2	58.4	337
Patient 7	118	59.8	128	48.8	205
Patient 8	91.8	10.8	14.2	52	102
100 µg kg^{-1}					
Patient 1	118	74	137	129	404
Patient 2	438	2470	1132	1042	798
Patient 3	103	29.2	53.9	75	197
Patient 4	40.9	54.2	45.6	56.9	168
Patient 5	103	20.3	31.5	59.7	41.7
Patient 6	64	53.4	177	177	288
Patient 7	117	33.9	77.5	159	714
Patient 8	119	13.2	25	38.2	144
150 µg kg^{-1}					
Patient 1	336	849	694		
Patient 2	339	152	107	80.1	19.6
Patient 3	40.9	39.5	41.5	248	347
Patient 4	75.3	50.8	62.1	96.2	50.8
Patient 5	218	44.3	85	110	1708
Patient 6	231	29.5	30.3	31.9	133
Patient 7	212	44.3	43.6	119	169
Patient 8	110	17.5	36.4	55.3	253

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Inspired oxygen fraction after cardiopulmonary bypass: effects on pulmonary function with regard to endothelin-1 concentrations and venous admixture

A. Reber[1]*, B. Budmiger[1], M. Wenk[2], W. E. Haefeli[2], T. Wolff[3], T. Bein[4] and K. Skarvan[1]

[1]Department of Anaesthesia, [2]Department of Clinical Pharmacology and [3]Department of Cardiothoracic Surgery, University of Basel/Kantonsspital, CH-4031 Basel, Switzerland. [4]Department of Anaesthesiology, University Hospital, D-93042 Regensburg, Germany

**Corresponding author*

Twenty consecutive patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) were allocated at random to group 1 (*n*=10, high inspired oxygen fraction ($F\text{I}_{O_2}$) after CPB), or group 2 (*n*=10, moderate $F\text{I}_{O_2}$ after CPB). The effects of each $F\text{I}_{O_2}$ on arterial and mixed venous concentrations of endothelin-1 (ET-1) and its precursor, Big ET-1, were measured. Venous admixture was calculated to assess the efficiency of pulmonary gas exchange. Patients whose lungs had been ventilated with a $F\text{I}_{O_2}$ of 1.0 (exposure time 70 min) after weaning from the CPB machine had significantly greater arterial and mixed venous Big ET-1 concentrations and venous admixture than patients whose lungs were ventilated with a $F\text{I}_{O_2}$ of 0.35. In contrast, ET-1 concentrations in the two groups were not significantly different. A reduction of $F\text{I}_{O_2}$ from 1.0 to 0.6 reduced venous admixture without lowering endothelial peptide concentrations. On the first postoperative day all peptide concentrations were similar in the two groups, whereas venous admixture remained non-significantly higher in group 1. A short period of high $F\text{I}_{O_2}$ immediately after CPB increases endothelin concentrations and pulmonary venous admixture.

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Anaesthesia adversely affects pulmonary function by affecting respiratory system mechanics and gas exchange in the lungs. Impaired oxygenation of the blood occurs in most subjects who are anaesthetized.[1 2] Cardiac surgery with the use of extracorporeal circulation is frequently associated with impaired ability of the lungs to oxygenate blood.[3 4] It has therefore become routine to increase the inspired oxygen fraction ($F\text{I}_{O_2}$) in order to prevent hypoxaemia. Hyperoxygenation generates oxygen radicals and consequently may increase reoxygenation injury after cardiopulmonary bypass (CPB). The superoxide anion may be an important factor in this damage.[5] Hyperoxygenation can also increase ventilation–perfusion inequalities and alveolar collapse.[6 7] After lung collapse, blood flow, and probably blood volume, are reduced because of hypoxic pulmonary vasoconstriction.[8] Both local accumulation of oxygen radicals and local hypoxic pulmonary vasoconstriction may influence regional pulmonary integrity. Recent studies suggest that, of the endothelium-derived factors, endothelin-1 (ET-1), a potent vasoconstrictor, may be an important mediator of hypoxic pulmonary vasoconstriction.[9] Its precursor, Big ET-1, could be an even more sensitive measure of endothelial dysfunction.[10] Hyperoxaemic normothermic CPB can have adverse effects on tissue oxygenation,[11] and uncontrolled reoxygenation results in marked production of conjugated diene as a sign of oxidant damage.[12] This damage may increase plasma ET-1 concentrations, as the same increase has been found in patients at risk of developing acute lung injury[13] Reoxygenation damage seems to depend on oxygen tension.[14] Reducing $F\text{I}_{O_2}$ may be less effective than hyperoxygenation in preventing tissue hypoxaemia. On the other hand, partial denitrogenation can reduce tissue damage and prevents or reduces ventilation–perfusion mismatching[6 7] We hypothesized that a short period of increased $F\text{I}_{O_2}$ immediately after CPB has a detrimental effect on both endothelium-derived factors and pulmonary gas exchange.

Materials and methods

Study population

The study was approved by the Ethics Committee of the University Hospital of Basel and written informed consent was obtained from each patient. Patients with significant

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pulmonary, endocrine, renal, metabolic or neurological disease were excluded from the study. We also excluded emergency patients and patients requiring preoperative intravenous inotropic drugs, intra-aortic balloon support or mechanical ventilation. Sealed envelopes were used to allocate at random 20 consecutive adults undergoing cardiac surgery with CPB to group 1 (n=10, high $F\text{I}_{O_2}$ (1.0)) or group 2 (n=10, moderate $F\text{I}_{O_2}$ (0.35)).

Table 1 Study plan for blood sampling, and measurements obtained CPB, cardiopulmonary bypass; $F\text{I}_{O_2}$, inspired oxygen fraction; ICU, intensive care unit

Time	$F\text{I}_{O_2}$ for group 1	$F\text{I}_{O_2}$ for group 2
During anaesthesia before CPB	0.5	0.5
20 min after weaning from CPB machine	1.0	0.35
90 min after arrival in the ICU	0.6	0.6
After extubation of patient's trachea (day 1)	0.4	0.4

Anaesthetic technique and surgery

Premedication consisted of morphine 0.1 mg kg^{-1} and scopolamine 0.004 mg kg^{-1} i.m. before transfer to the operating room. Anaesthesia was induced with fentanyl (10 µg kg^{-1}) and midazolam (0.1–0.15 mg kg^{-1}) or hypnomidate (0.02 mg kg^{-1}). To facilitate intubation of the patient's trachea, muscular paralysis was achieved with pancuronium (0.1 mg kg^{-1}). Anaesthesia was maintained with additional doses of fentanyl and midazolam combined with isoflurane (end-tidal concentration 0.2–0.8 vol%) if necessary. When further doses of neuromuscular blocking agents were required, i.v. pancuronium 2 mg was used. Routine cardiac monitoring included leads II and V5 of the electrocardiogram, pulse oximetry, capnography, oesophageal and rectal temperatures, a 20-G radial artery catheter and a three-lumen 7.5 Fr pulmonary artery catheter (Baxter, Irvine, CA, USA) inserted through the right internal jugular vein. Intravascular systemic and pulmonary artery pressures, heart rate and arterial and mixed venous oxygen partial pressures were recorded (PCMS Workstation 19845-15-03; Spacelabs, Chatsworth, CA, USA). All patients were ventilated mechanically at a rate of 6 breath min^{-1} with air–oxygen mixture ($F\text{I}_{O_2}$=0.5) using a Sulla 808V ventilator with a circle system 8 ISO (Drägerwerke, Lübeck, Germany) and a Ventilog ventilator (Drägerwerke) with zero end-expiratory pressure. Tidal volume was 8–15 ml kg^{-1} to maintain end-tidal $P\text{CO}_2$ at 4.5–4.9 kPa. No further changes in ventilation were made before CPB. Operations were performed with standardized CPB (SARNS 9000; Terumo Cardiovascular System, Ann Arbor, MI, USA) including repeated cold-blood cardioplegia, hollow-fibre membrane oxygenator (Affinity Oxygenator; Medtronic Inc, Minneapolis, MN, USA) with a 40-µ filter in the arterial flow and mild systemic hypothermia (above 32°C) maintained during aortic cross-clamping. The methods of cannulation and heart preservation used were at the surgeon's discretion and did not differ between groups. During surgery, intravascular volume replacement was achieved with lactated Ringer's solution. Packed red cells were administered to maintain haematocrit above 25% during CPB and above 28% afterwards. The residual volume of the circuit was retransfused. After the patient was rewarmed and weaned from the CPB machine, $F\text{I}_{O_2}$ was set to either 1.0 (high, group 1) or 0.35 (moderate, group 2) with a mean exposure time of 70 min (Table 1). Except for the $F\text{I}_{O_2}$, the ventilatory mode did not differ from the pre-bypass settings in order to preserve equal ventilatory conditions between the groups. Anaesthesia was maintained with additional boluses of fentanyl and midazolam. After surgery, patients were transferred to the intensive care unit (ICU) and ventilated mechanically with an $F\text{I}_{O_2}$ of 0.6 in both groups. Intravenous fentanyl and midazolam were used for analgesia and sedation. Postoperative care was standardized for all patients and extubation was accomplished at the earliest clinically appropriate time after the patient had been weaned from pressure-support ventilation. Criteria for extubation included being conscious, normothermia, haemodynamic stability, adequate pulmonary function with a respiratory rate between 10 and 20 breath min^{-1} and satisfactory blood gases, adequate urine output and minimal chest tube output.

Blood sampling

Blood samples were obtained from the distal lumen of the pulmonary artery catheter and from the cannula in the radial artery. Peptide concentrations and calculations determining venous admixture (see below) were based on analyses of these blood samples, which were obtained at the following times: (i) during anaesthesia before surgery (baseline); (ii) 20 min after CPB had been discontinued, before sternal closure; (iii) 90 min after arrival in the ICU; (iv) on the first postoperative day in the ICU (Table 1).

Peptide analyses

Freshly collected blood was anticoagulated with ethylenediamine tetraacetate and put on ice immediately, and centrifuged within 1 h to separate plasma. The plasma samples were stored at –70°C and mixed well before assaying. For ET-1 and Big ET-1 analyses, a sandwich-type enzyme immunoassay (Biomedica, Vienna, Austria) was used. Direct measurements of the peptides were performed in duplicate according to the manufacturer's instructions. To provide maximum sensitivity, the kits for ET-1 and Big ET-1 had highly specific immunoaffinity-purified polyclonal capture antibodies and monoclonal detection antibodies. In the first step, sample and monoclonal detection antibody were added simultaneously to microtitre plate wells precoated with capture antibody. Big ET-1 and ET-1, if present in the sample, bound and formed a sandwich with the detection antibody. After a washing step, which removed non-specifically bound material, a peroxidase-conjugated antibody detected the presence of bound detection antibodies. After removal of unbound conjugate by washing, tetramethylbenzidine was added to the wells as a substrate. Big ET-1 and ET-1 were quantified by an enzyme-catalysed colour change detectable using a standard ELISA reader. The amount of colour was directly proportional to the amount of ET-1 and Big ET-1 present in the sample. The concentration range of quality control samples was between 2 and 6 fmol ml^{-1}, with intra- and interassay coefficients of variation of 2.5–5.5 and 3.2–10.9% respectively. The detection limit for Big ET-1 was 0.1 fmol $litre^{-1}$ and for ET-1 it was 0.2 fmol $litre^{-1}$.

Venous admixture

The amount of venous admixture as a percentage of the total flow (Qs/Qt)×100) was calculated from the standard equation $Qs/Qt = (CcO_2 - CaO_2)/(CcO_2 - CvO_2)$, where CcO_2 = end-pulmonary capillary oxygen content, CaO_2 = arterial oxygen content and CvO_2 = mixed venous oxygen content.[15 16] Arterial and mixed venous blood gas measurements were performed by using a standard technique with the electrodes calibrated for the required partial pressure ranges (ABL 500; Radiometer, Copenhagen, Denmark). The end-pulmonary capillary oxygen content was calculated by using the equation for the alveolar oxygen partial pressure as follows: $PA_{O_2} = ((760 \text{ mm Hg} - 47 \text{ mm Hg}) \times FI_{O_2}) - (PA_{CO_2} \times 1.25)$, where PA_{CO_2} is the arterial carbon dioxide partial pressure. Arterial and mixed venous oxygen saturations and haemoglobin were performed by haemoximetry (OSM2, Copenhagen, Denmark). To assess oxygenation when FI_{O_2} was varied, the oxygenation index (PA_{O_2}/FI_{O_2} ratio) was also calculated.

Statistical analyses

Multiple comparisons were performed by the use of Friedman analysis of variance for repeated measures. Groups were compared by the use of the Wilcoxon rank-sum test. For *post hoc* comparisons, Tukey's test was applied if appropriate and probability values were calculated. The Spearman rank correlation coefficient (r_s) was used to analyse relationships between variables. A P value of less than 0.05 was considered significant. For all calculations, the Statistica/v 4.5 software package (StatSoft, Tulsa, OK, USA) was used.

Results

Patient details before CPB are presented in Table 2. There was no correlation between patient characteristics and measured clinical data.

Effects of high FI_{O_2} immediately after CPB

Ventilating the patient's lungs with a FI_{O_2} of 1.0 after weaning from the CPB machine (group 1) resulted in significantly greater arterial and mixed venous Big ET-1 concentrations (2.6±1.2 and 2.7±1.2 fmol $litre^{-1}$ respectively) compared with patients who received a moderate FI_{O_2} of 0.35 (1.4±0.4 fmol $litre^{-1}$ for both Big ET-1 concentrations) (group 2) ($P < 0.05$) (Fig. 1). In contrast, ET-1 concentrations in the two groups were not significantly different (Fig. 1). In addition in group 1, arterial and mixed venous ET-1 concentrations were significantly greater during hyperoxygenation than before bypass, whereas group 2 showed no difference in ET-1 concentrations between the bypass and pre-bypass values.

In group 1, venous admixture was significantly greater during hyperoxygenation (20.9±7.5%) than before bypass (8.1±3.8%), whereas group 2, with a moderate FI_{O_2} of 0.35, showed no significant difference for this variable (Fig. 1). The PA_{O_2}/FI_{O_2} ratio after CPB was significantly greater in group 1 (310±157 mm Hg) than in group 2 (225±43 mm Hg) ($P < 0.05$).

Pre-bypass values of pulmonary artery pressures were significantly greater in group 1 (25±5) than in group 2 (19±4), but were similar after CPB (23±6 *vs* 20±8). Peptide concentrations did not correlate with haemodynamic variables, except for a weak, non-significant correlation in group 1 between arterial ET-1 and pulmonary artery pressure (r_s=0.60), and between mixed venous ET-1 concentration and right atrial pressure (r_s=0.60) after CPB. There was no correlation between peptide concentrations and venous admixture.

Changing the FI_{O_2} from 1.0 (group 1) and 0.35 (group 2) to 0.60 in both groups resulted in no significant changes in peptide concentrations and venous admixture in the ICU. In group 1, however, mixed venous and arterial ET-1 and Big ET-1 values remained significantly increased compared with the pre-bypass values despite reduction of the FI_{O_2} (Fig. 1). There were no significant differences in peptide values between the groups.

Prolonged effects of high FI_{O_2} after CPB

On the first postoperative day, peptide concentrations were similar in the two groups (Fig. 1). However, venous admixture remained slightly greater in group 1 (6.3±2.6) than in group 2 (4.5±2.4), although the difference was not significant ($P = 0.12$). Extubation times were similar in the two groups (756±253 min after intubation in group 1 *vs* 764±243 min in group 2). The PA_{O_2}/FI_{O_2} ratio, respiratory variables and time of discharge from the ICU did not differ significantly between the two groups.

Discussion

We found that a short period of increased FI_{O_2} immediately after CPB affected endothelial and gas exchange function. Big ET-1 concentrations and venous admixture after hyperoxygenation were significantly greater compared with pre-bypass values and the group with the moderate FI_{O_2} of 0.35. A reduction of FI_{O_2} from 1.0 to 0.6 decreased venous admixture without lowering endothelial peptide values.

Big ET-1 concentrations were elevated during exposure of the lungs to pure oxygen. Because Big ET-1 is the precursor of ET-1, pulmonary endothelial integrity may

Table 2 Clinical characteristics of the patients undergoing CPB. Data are (mean (SD) or range) Statistical analysis revealed no significant difference between the two study groups except for the sex of the groups (preponderance of males in group 1) *Weight height^{-2}; †baseline (pre-bypass) values

	Study conditions	
	High $F\text{I}_{O_2}$ (group 1)	**Moderate $F\text{I}_{O_2}$ (group 2)**
Sex (M/F)	9/1	5/5
Age (yr)	68 (53–81)	65 (46–80)
Body mass index* (kg m^{-2})	27.1 (5.5)	25.7 (5.0)
Body surface area (m^2)	1.9 (0.2)	1.8 (0.2)
Systemic arterial pressure mean† (mm Hg)	79 (9)	79 (19)
Right atrial pressure mean† (mm Hg)	10 (4)	9 (5)
Pulmonary artery pressure mean† (mm Hg)	25 (5)	19 (5)
$<\text{PaO}_2>/F\text{I}_{O_2}$† (mm Hg)	331 (119)	363 (75)
Coronary artery surgery	1	4
Aortic valve or mitral valve surgery	9	6
Cardiopulmonary bypass times (min)	116 (34)	84 (38)
Time between completion of CPB and arrival in the ICU (min)	70 (15)	76 (26)

be altered by hyperoxygenation. In our patients, the increase in peptide values was not as great as that seen in patients at risk of developing acute lung injury, where ET-1 values were significantly elevated.[13 17] None of these studies measured changes in Big ET-1. The physiological significance of Big ET-1 is still not clear, but Big ET-1 may be a more sensitive indicator of endothelial changes when compared with ET-1.[10] Nonetheless, the present findings call for a re-evaluation of hyperoxygenation, a practice that generates oxygen radicals[18] and could worsen re-oxygenation injuries. The superoxide anion may be a central agent for this damage, especially because re-oxygenation is associated with a burst of superoxide anions[5] and CPB *per se* may generate reactive oxygen intermediates.[19] Endothelial cells exposed to hyperoxia for 30 min produce free radicals via mitochondrial electron transport mechanisms.[20] Adverse effects on tissue oxygenation during hyperoxaemic normothermic CPB are known,[11] and uncontrolled re-oxygenation results in marked production of conjugated dienes as a sign of oxidant damage.[12] In our patients, no measure of lipid hydroperoxide formation as an indicator of oxidant stress was included,[12] but oxidant damage may increase plasma ET-1 concentrations.[13] We do not know if the increased plasma peptide concentrations were caused by increased production, decreased pulmonary extraction or both. The lungs are exposed to virtually all of the cardiac output and thus contain oxygen radicals and released ET-1. Alterations of pulmonary function with increased venous admixture may alter net clearance or production of ET-1 by the lungs. If the adverse effects of oxygen caused by hyperoxia can be more clearly attributed to tissue oxygenation, we suggest that hyperoxia should be avoided and $F\text{I}_{O_2}$ should be reduced.

In our study, intrapulmonary shunt was assessed by using the oxygen technique, and included regions with low ventilation/perfusion ratios. Thus, the 'oxygen shunt' was not a pure shunt and we therefore call it 'venous admixture'. However, it is known that after CPB, regions with low ventilation/perfusion ratios are relatively small compared with true shunt (5 *vs* 27% of cardiac output).[21] We calculated this shunt, as we did for the single measurement after CPB, during pure oxygen breathing, which eliminated any contribution to the shunt value from regions with low ventilation/perfusion ratios. The oxygen content of pulmonary capillary blood was calculated from alveolar oxygen tension. The difference between capillary and arterial content could have been artefactually increased because one of these values was calculated (as a high oxygen partial pressure) and the other variables from the shunt equation were measured. Although the oxygen technique has limitations in the description of intrapulmonary shunt, our calculated venous admixture data varied clearly with different $F\text{I}_{O_2}$. In addition, for our clinical trial the oxygen technique was less complex and costly compared with other techniques using inert tracer gases.

Arterial plasma ET-1 concentration has a small but significant correlation with pulmonary arterial pressure.[22] Arterial ET-1 also correlates directly with right atrial pressure, pulmonary vascular resistance to systemic vascular resistance ratio, peak airway pressure and airway resistance.[22] The non-significant correlation between plasma ET-1 values and pulmonary artery pressure is consistent with other studies in which ventilation of the lung with 100% oxygen had no significant acute effect on vascular resistance in the normal human lung.[23] Pulmonary arterial pressure values were not equal in the two groups before CPB, indicating the difficulty of getting a good match in this kind of a study. Data obtained during different oxygenation regimes after CPB showed similar pressure values, suggesting no acute effect of post-bypass hyperoxia on vascular resistance. Other possible effects of hyperoxia, such as inhibition of flow in lymphatic vessels that can affect extravascular lung water and thus influence pulmonary integrity, were not analysed in our study and could also change pulmonary function.[24]

Our results suggest that decreasing intraoperative $F\text{I}_{O_2}$ was sufficient to reduce alveolar collapse and subsequent pulmonary shunt, and suggest caution in using high $F\text{I}_{O_2}$ after weaning from CPB. Interestingly, a reduction of $F\text{I}_{O_2}$

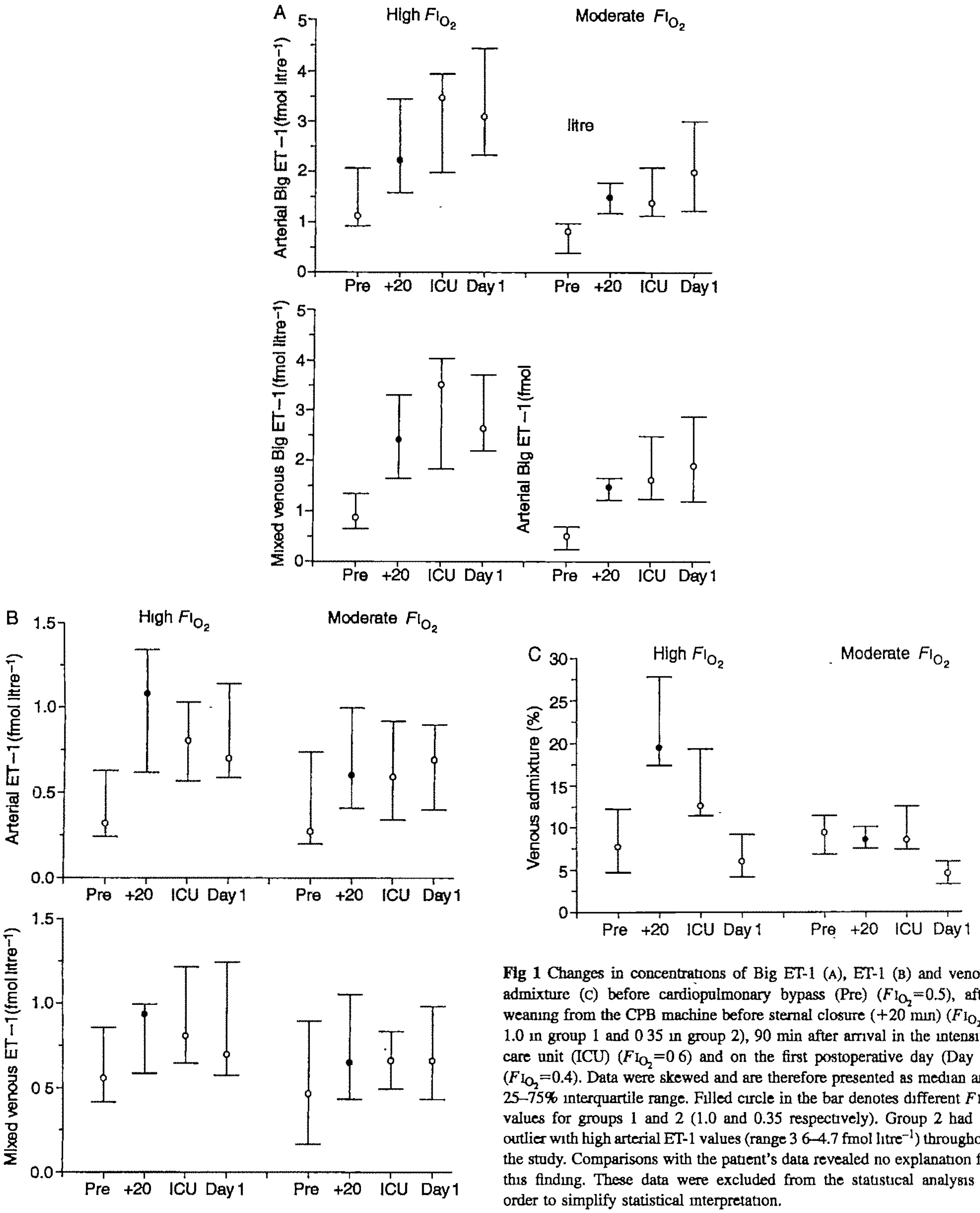

Fig 1 Changes in concentrations of Big ET-1 (A), ET-1 (B) and venous admixture (C) before cardiopulmonary bypass (Pre) ($F_{I_{O_2}}$=0.5), after weaning from the CPB machine before sternal closure (+20 min) ($F_{I_{O_2}}$= 1.0 in group 1 and 0.35 in group 2), 90 min after arrival in the intensive care unit (ICU) ($F_{I_{O_2}}$=0.6) and on the first postoperative day (Day 1) ($F_{I_{O_2}}$=0.4). Data were skewed and are therefore presented as median and 25–75% interquartile range. Filled circle in the bar denotes different $F_{I_{O_2}}$ values for groups 1 and 2 (1.0 and 0.35 respectively). Group 2 had an outlier with high arterial ET-1 values (range 3.6–4.7 fmol litre^{-1}) throughout the study. Comparisons with the patient's data revealed no explanation for this finding. These data were excluded from the statistical analysis in order to simplify statistical interpretation.

from 1.0 to 0.6 reduced venous admixture without lowering endothelial peptide concentrations. It is obvious that lowering $F_{I_{O_2}}$ can increase the risk of hypoxaemia. Twenty minutes after CPB, blood gas analysis in five patients ventilated with a $F_{I_{O_2}}$ of 0.35 revealed a range of $P_{A_{O_2}}$ from 7.7 to 10.3 kPa, resulting in arterial oxygen saturation between 90 and 97%. However, acid–base balance was not severely affected, with a pH between 7.28 and 7.52.

Although venous admixture remained slightly greater in group 1 than in group 2 on the first postoperative day, there was no difference in outcomes, such as time to extubation. However, it should be stressed that the time to extubation is influenced by many factors and cannot be used as an index of equal pulmonary integrity in the two groups in the present study.

In conclusion, a short period of high $F\mathrm{I}_{\mathrm{O}_2}$ immediately after CPB changes endothelial peptide and gas exchange. The considerable increase in venous admixture associated with hyperoxia and its prolonged effect on pulmonary function, which persisted in our patients even on the first postoperative day, contrasts with the expected advantages of this procedure. The relationship between the oxygen-induced increase in peptide plasma concentration and pulmonary gas exchange may not be direct. More complex mechanisms may be involved, which require further investigation for their clarification.

References

1 Nunn JF, Bergman NA, Coleman AJ. Factors influencing the arterial oxygen tension during anaesthesia with artificial ventilation. *Br J Anaesth* 1965; **37**: 898–914

2 Sykes MK, Young WE, Robinson BE. Oxygenation during anaesthesia with controlled ventilation. *Br J Anaesth* 1965; **37**: 314–25

3 Andersen NB, Ghia J. Pulmonary function, cardiac status, and postoperative course in relation to cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1970; **59**: 474–83

4 Braun SR, Birnbaum ML, Chopra PS. Pre- and postoperative pulmonary function abnormalities in coronary artery revascularization surgery. *Chest* 1978; **3**: 316–20

5 Buckberg GD. Studies of hypoxemic/reoxygenation injury: I. Linkage between cardiac function and oxidant damage. *J Thorac Cardiovasc Surg* 1995; **110**: 1164–70

6 Rothen HU, Sporre B, Engberg G, Wegenius G, Reber A, Hedenstierna G. Prevention of atelectasis during general anaesthesia. *Lancet* 1995; **345**: 1387–91

7 Reber A, Engberg G, Wegenius G, Hedenstierna G. Lung aeration. The effect of pre-oxygenation and hyperoxygenation during total intravenous anaesthesia. *Anaesthesia* 1996; **51**: 733–7

8 Marshall BE, Marshall C, Frasch F, Hanson CW. Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution. *Intensive Care Med* 1994; **20**: 291–7

9 Stewart DJ. Endothelin in cardiopulmonary disease: factor paracrine vs. neurohumoral. *Eur Heart J* 1993; **14**: 48–54

10 Nelson JB, Opgenorth TJ, Fleisher LA, Frank SM. Perioperative plasma endothelin-1 and Big endothelin-1 concentrations in elderly patients undergoing major surgical procedures. *Anesth Analg* 1999; **88**: 898–903

11 Joachimsson PO, Sjoberg F, Forsman M, Johansson M, Ahn HC, Rutberg H. Adverse effects of hyperoxemia during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1996; **112**: 812–9

12 Morita K, Ihnken K, Buckberg GD. Studies of hypoxemic/reoxygenation injury with aortic clamping: XII. Delay of cardiac reoxygenation damage in the presence of cyanosis: a new concept of controlled cardiac reoxygenation *J Thorac Cardiovasc Surg* 1995; **110**: 1265–73

13 Boldt J, Menges T, Kuhn D, Diridis C, Hempelmann G. Alterations in circulating vasoactive substances in the critically ill–a comparison between survivors and non-survivors. *Intensive Care Med* 1995; **21**: 218–25

14 Ihnken K, Morita K, Buckberg GD, Young HH. Studies of hypoxemic/reoxygenation injury with aortic clamping: XI. Cardiac advantages of normoxemic versus hyperoxemic management during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1995; **110**: 1255–64

15 Berggren SM. The oxygen deficit of arterial blood caused by non-ventilating parts of the lung. *Acta Physiol Scand* 1992; **4** (Suppl): 1–92

16 Räsanen J, Downs JB, Malec DJ, DeHaven B, Garner WL. Real-time continuous estimation of gas exchange by dual oximetry. *Intensive Care Med* 1988; **14**: 118–22

17 Langleben D, Demarchie M, Laporta D, *et al.* Endothelin-1 in acute lung injury and the adult respiratory distress syndrome. *Am Rev Resp Dis* 1993; **148**: 1646–50

18 Freeman BA, Crapo JD. Hyperoxia increases oxygen radical production in rat lungs and lung mitochondria. *J Biol Chem* 1981; **256**: 10986–92

19 Bolli R, Jeroudi MO, Patel BS. Direct evidence that oxygen-derived free radicals contribute to postischemic myocardial dysfunction in the intact dog. *Proc Natl Acad Sci USA* 1989; **86**: 4695–9

20 Sanders SP, Zweier JL, Kuppusamy P, *et al.* Hyperoxic sheep pulmonary microvascular endothelial cells generate free radicals via mitochondrial electron transport. *J Clin Invest* 1993; **91**: 46–52

21 Hachenberg T, Tenling A, Nystrom SO, Tyden H, Hedenstierna G. Ventilation–perfusion inequality in patients undergoing cardiac surgery. *Anesthesiology* 1994; **80**: 509–19

22 Mitaka C, Hirata Y, Nagura T, Tsunoda Y, Amaha K. Circulating endothelin-1 concentrations in acute respiratory failure. *Chest* 1993; **104**: 476–80

23 Hambraeus-Jonzon K, Bindslev L, Mellgård ÅJ, Hedenstierna G. Hypoxic pulmonary vasoconstriction in human lungs. *Anesthesiology* 1997; **86**: 308–15

24 Hachenberg T, Tenling A, Rothen HU, Nystrom SO, Tyden H, Hedenstierna G. Thoracic intravascular and extravascular fluid volumes in cardiac surgical patients. *Anesthesiology* 1993; **79**: 976–84

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Assessment of the adequacy of systemic and regional perfusion after cardiac surgery

S. M. Jakob*, E. Ruokonen and J. Takala

Critical Care Research Program, Department of Anesthesiology and Intensive Care, Kuopio University Hospital, FIN-70210 Kuopio, Finland

**Corresponding author: Divison of Intensive Care, Kuopio University Hospital, PO Box 1777, FIN-70211 Kuopio, Finland*

Changes in systemic, hepatosplanchnic and femoral blood flow and liver function after cardiac surgery were studied in 17 patients from April to October 1995. Blood flows were measured every 3 h and gastric mucosal $P\text{CO}_2$ (by tonometry) every hour from arrival in the intensive care unit until extubation. Cardiac output and systemic oxygen consumption increased from 2.83 (0.68) litres min^{-1} m^{-2} to 3.17 (0.57) litres min^{-1} m^{-2} and from 126 (18) ml min^{-1} m^{-2} to 135 (44) ml min^{-1} m^{-2}, respectively (mean (SD), P=0.028 and P=0.019, respectively, baseline *vs* 6 h). The fraction of cardiac output distributed to the splanchnic region decreased from 0.25 (0.06) to 0.20 (0.04) (P=0.004) while splanchnic oxygen extraction increased from 0.43 (0.15) to 0.50 (0.12) (P=0.019). Femoral blood flow increased from 0.18 (0.07) litres min^{-1} m^{-2} to 0.23 (0.09) litres min^{-1} m^{-2}, (P=0.006, baseline *vs* 3 h) but femoral oxygen consumption did not change. Changes in blood flow were not reflected by venous–arterial $P\text{CO}_2$ gradients. Initially high glutathione transferase alpha concentrations decreased and indocyanine green extraction was well preserved. We conclude that the predominant increase in peripheral blood flow and the increased oxygen uptake in certain regions of the body may increase the risk of a mismatch between splanchnic perfusion and metabolic demands. This mismatch was not associated with impaired liver function or cellular integrity.

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The postoperative course after cardiopulmonary bypass is uneventful in the vast majority of patients. Morbidity and mortality, though rare,[1 2] are associated with substantial cost.[3] Gastrointestinal hypoperfusion has been associated with the development of postoperative complications.[4] Even patients with an uneventful postoperative course are predisposed to inadequate splanchnic perfusion as demonstrated by peri- and postoperative high splanchnic oxygen extraction and gastric mucosal acidosis.[5–7] Low blood flow is likely to contribute but interventions aimed at increasing blood flow have had inconsistent results. Perioperative volume loading seems to prevent or ameliorate mucosal acidosis and outcome.[4] Increasing systemic blood flow does not prevent a decrease in gastric mucosal blood flow.[8] Postoperative angiotensin converting enzyme inhibition does not increase total splanchnic blood flow but worsens mucosal acidosis.[9] Dobutamine and dopexamine may, paradoxically, decrease gastric mucosal pH despite an increased total splanchnic blood flow.[6 10] The pathogenesis, functional consequences and clinical relevance of splanchnic hypoperfusion after cardiac surgery are thus poorly understood. Except for tonometry, indices of splanchnic perfusion and the possible functional consequences of prolonged hypoperfusion have not been studied longitudinally. The effect of complex changes in physiological variables (for example, acid–base status, haemoglobin content, oxygen extraction and carbon dioxide production) on the relation between $P\text{CO}_2$ and carbon dioxide content have to be taken into account in the interpretation of changes in systemic, regional or local mucosal $P\text{CO}_2$ gradients. The effect of weaning patients from mechanical ventilation may also have profound effects on mucosal perfusion as assessed by tonometry.[11] The assessment of changes in systemic and regional perfusion in cardiac surgery patients from intensive care unit (ICU) admission until extubation together with regional and local markers of oxygenation, metabolism and cellular integrity may improve the understanding of the pathogenesis of splanchnic hypoperfusion after cardiopulmonary bypass, and help to identify those patients at risk for development of serious complications. Furthermore,

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different reasons for apparent gastric mucosal acidosis may be identified, which may help in the interpretation of tonometry-derived variables in other patient groups. The aims of this study were, therefore: (i) to describe longitudinal changes in systemic and regional perfusion and metabolism after cardiac surgery, including the impact of weaning from mechanical ventilation, and to assess their effect on liver function and cellular integrity, and (ii) to determine potential causes of increased mucosal $P\text{CO}_2$ by establishing the relation between regional carbon dioxide production, $P\text{CO}_2$ and carbon dioxide content.

Methods

The study was approved by the ethics committee of the hospital and written informed consent was obtained from each patient. Seventeen patients were studied after coronary bypass surgery. Inclusion criteria were: elective surgery, stable cardiac function without clinical signs of heart failure, lack of symptomatic cerebral or peripheral vascular disease. Systemic (pulmonary artery catheter), hepatosplanchnic and femoral (dye dilution) haemodynamics and oxygen transport were measured every 3 h and gastric mucosal $P\text{CO}_2$ (tonometry) every hour during the first 12 h in the ICU or until extubation, whichever was shorter.

Anaesthesia was standardized as previously described.[6] Briefly, anaesthesia was induced and maintained by fentanyl, midazolam, alcuronium and pancuronium, and supplemented by thiopental and halothane. Cardiopulmonary bypass with a nonpulsatile flow rate of 2–2.7 litres min^{-1} m^{-2} was used. Systemic hypothermia (32–34°C) and topical myocardial hypothermia and hyperkalaemic cardioplegia were used. Patients were weaned from cardiopulmonary bypass when rectal temperature was $\geq$34°C. Phenylephrine was used to achieve a mean arterial pressure of 50–55 mm Hg during cardiopulmonary bypass. Sedation in the ICU was maintained at a Ramsay score[12] of 3 until stable haemodynamics were achieved. If needed, boluses of thiopental and oxycodone were given. In five patients, postoperative systolic arterial pressure of $\geq$160 mm Hg was treated with sodium nitroprusside. If shivering occurred, vecuronium was used. Crystalloids and colloids (hydroxyethylstarch, Plasmafusin 6%; Pharmacia–Upjohn, Helsinki, Finland) were infused to maintain the pulmonary capillary wedge pressure at the level that was assessed clinically to be optimal for cardiac performance. The patients' lungs were mechanically ventilated with an $F\text{I}_{\text{O}_2}$ of 0.4–0.5 and a PEEP of 5 cm H_2O until the haemodynamics and peripheral circulation had stabilized. Afterwards sedation was stopped and the ventilator mode switched to pressure support. Patients were extubated if they had reached a Ramsay score of 2, were haemodynamically stable, were on pressure support ventilation with $\leq$8 cm H_2O, showed no clinical signs of distress and had normal arterial blood gases. Systemic oxygen consumption and carbon dioxide production were measured by indirect calorimetry (Deltatrac; Datex–Ohmeda, Helsinki, Finland). For comparison of values before and after extubation, oxygen consumption was calculated according to the Fick principle.

Regional blood flows were estimated by a primed continuous infusion of indocyanine green (Cardiogreen; Becton–Dickinson Microbiology Systems, Cockeysville, MD, USA) as previously described.[13] In the present study, mean (SD) indocyanine green extraction (which may also be used as a measure of liver function) was 78.5 (11.4) %; the coefficient of variation for the three consecutive blood flow measurements at 20, 25 and 30 min during each infusion of indocyanine green was 9.1 (8.8) % and 3.4 (4.1) % for splanchnic and femoral blood flow, respectively.

Cardiac output was measured by thermodilution (mean of three measurements). Arterial $P\text{CO}_2$, oxygen saturation and haemoglobin were measured by co-oximetry (ABL 500 and OSM3; Radiometer, Copenhagen, Denmark) and systemic and regional oxygen delivery were calculated as the product of arterial oxygen content and blood flow. Regional oxygen consumption was calculated as the product of regional blood flow and arterial–venous oxygen content. Systemic and regional venous–arterial carbon dioxide contents were calculated using an iterative procedure as proposed by Giovannini and colleagues[14] (see Appendix).

Gastric mucosal $P\text{CO}_2$ was measured hourly by gastric tonometry (Tonomitor; Tonometrics, Worcester, MA, USA) after 60–90 min of equilibration (first measurement; thereafter after 60 min of calibration), and analysed with the same blood gas analyser as used for the blood samples (ABL 500; Radiometer). The values were corrected according to the blood temperature. Correct positioning of the catheter was confirmed by fluoroscopy. H_2-receptor antagonists were not given. The upper normal limit (mean + 1.96 SD) for gastric mucosal–arterial $P\text{CO}_2$ gradients obtained from 12 healthy volunteers whose gastric acid secretion had been inhibited with H_2-antagonists was 3.24 kPa (recalculated from the original data of Parviainen and colleagues[15]). Plasma lactate was measured by an amperometric enzyme sensor method (YSI 2300 Stat Plus; YSI Incorporated, Yellow Springs, OH, USA), and whole blood pyruvate by an enzymatic colour reaction (Sigma UV-706; Sigma Diagnostics, St Louis, MO, USA) and spectrophotometry (Shimadzu CL-750; Shimadzu Corporation, Kyoto, Japan). According to the literature, normal lactate/pyruvate (L/P) ratios are <10–15. We measured arterial (plasma) lactate and (whole blood) pyruvate in a group of 22 healthy volunteers. Their mean (SEM) L/P ratio was 11.0 (0.3). The reference range, calculated as proposed by Solberg,[16] yielded an upper normal limit (mean + 1.96 SD) of 13.5.

Serum glutathione transferase alpha (GSTA) is a very sensitive marker in the assessment of hepatocellular integrity, both during and after liver transplantation and general anaesthesia.[17] [18] GSTA concentration was measured by an enzyme immunoassay (Hepkit-Alpha; Biotrin International, Dublin, Ireland) after storage at −70°C. The range of quantification of the assay was 100–2000 pg ml^{-1} (diluted five- to 10-fold). The upper normal limit (mean + 1.96 SD) for arterial samples, obtained separately for males and females from 10 healthy volunteers each, was 8.1 μg litre^{-1} (mean 4.4 μg litre^{-1}) for men, and 11.2 μg litre^{-1} (mean 4.1 μg litre^{-1}) for women.

Femoral artery and vein, and hepatic vein catheters and a gastric tonometer were inserted, in addition to systemic and pulmonary artery catheters, after admission to the ICU. The hepatic vein catheter was inserted via the right internal jugular vein, and correct positioning of the hepatic vein catheter and the gastric tonometer was confirmed by fluoroscopy and a small amount of contrast dye (hepatic vein catheter). Baseline measurements of haemodynamic variables, oxygen transport and mucosal $P\text{CO}_2$ were taken 2.65–4.25 h (median 3.35 h) after completion of extracorporeal circulation and then every third hour (mucosal $P\text{CO}_2$ every hour). At 20, 25 and 30 min after the start of the indocyanine green infusion, blood samples were drawn from the catheters for the analysis of blood gases, haemoglobin, haematocrit, lactate, pyruvate, indocyanine green and glutathione transferase alpha (the latter was measured at 20 and 30 min only). A saline sample from the tonometer for analysis of $P\text{CO}_2$ was taken at the end of each indocyanine green infusion.

Because of differences in the duration of mechanical ventilation, the number of measurement periods was different for individual patients. At least three measurements (i.e. up to 6 h) were taken in all 17 patients; 13 patients were studied during four measurement periods, and five patients during five measurement periods. The main analysis includes data from the first three measurement periods only. Haemodynamic variables and oxygen transport data were analysed from the individual measurement periods before and after extubation. Five patients received sodium nitroprusside during each measurement because of high systemic arterial pressure. These patients are marked separately in the figures.

Statistics

There were no significant differences in oxygen transport variables, local and systemic lactate, and venous–arterial $P\text{CO}_2$ gradients between patients with and without sodium nitroprusside. This was confirmed by analysis of variance (MANOVA) for repeated measurements and using sodium nitroprusside as a grouping factor. The patients were, therefore, considered to represent a single group. Changes over time were analysed by MANOVA, and differences between the measurements located by the Wilcoxon signed ranks test. The same test was used to analyse differences before and after extubation. P values of <0.05 were considered statistically significant. All results are presented as mean (SD) unless stated otherwise.

Table 1. Clinical data (n=17)

	Median	**Range**
Age (yr)	63	45–68
Angina pectoris NYHA	3	2–4
LVEF (%)	70	48–82
Number of anastomoses	5	2–7
Cardiopulmonary bypass time (min)	104	54–154
Aortic occlusion time (min)	92	42–134
Preoperative drugs	**Number of patients**	
Angiotensin converting enzyme inhibitors	4	
Beta blockers	17	
Nitrates	13	
Calcium antagonists	2	

Results

Clinical data are presented in Table 1. One patient arrived in the ICU with a sodium nitroprusside infusion because of high systemic arterial pressure, and four other patients received sodium nitroprusside later to treat arterial hypertension. Two patients were returned to the operating theatre because of bleeding, and two patients received temporary inotropic support because of low cardiac output after the study had been completed. All patients were discharged from the hospital on the sixth or seventh day after the operation. Cardiac output and femoral blood flow increased and the fractional splanchnic blood flow decreased (Table 2). Systemic oxygen consumption and carbon dioxide production increased. Splanchnic oxygen extraction increased, and femoral oxygen extraction decreased (Table 2). Arterial lactate increased minimally and remained within the normal range (Table 3). Regional but not arterial L/P ratios were high after admission to the ICU. While arterial and liver venous L/P ratios decreased, the femoral venous L/P ratio remained high. Both arterial and hepatic venous glutathione transferase alpha concentration was initially high but decreased later (Table 3). Indocyanine green extraction remained high (0.74 (0.14) at baseline, 0.82 (0.07) after 6 h; P=0.075). Systemic and splanchnic venous–arterial $P\text{CO}_2$ gradient increased, but venous–arterial carbon dioxide content did not (Table 3). Femoral venous–arterial $P\text{CO}_2$ gradient remained high, but femoral venous–arterial carbon dioxide content decreased. There was substantial within- and between-patient variability of gastric mucosal–arterial $P\text{CO}_2$ gradient. The highest gastric mucosal–arterial $P\text{CO}_2$ gradient was 1.94 (0.95) kPa; this occurred 4.0 (3.1) h after ICU admission.

Flow measurements after extubation were obtained from 11 patients (four patients had not yet been extubated 12 h after the first measurements, and two patients were returned to theatre; Table 4). Femoral blood flow decreased after extubation, but splanchnic blood flow did not change. While mucosal $P\text{CO}_2$ gradients remained stable (Table 4), indocyanine green extraction decreased slightly from 0.82 (0.08) to 0.72 (0.13) (P=0.013).

Discussion

There were three main findings. (i) Despite the high splanchnic oxygen extraction and the low and unchanged

Table 2. Haemodynamics, haemoglobin, temperature and oxygen transport variables ($n=17$, systemic $V\text{O}_2$ and $V\text{CO}_2$ $n=11$) Values are mean (SD). *P* time effect, multiple analysis of variance for repeated measurements $^*P<0.05$, $^†P<0.01$ *vs* ICU admission, Wilcoxon signed ranks sum test

	ICU admission	3 h	6 h	*P*
Heart rate (beat min^{-1})	81 (14)	84 (16)	82 (11)	0.612
MAP (mm Hg)	89 (8)	81 (9)	76 (11)	0.011
PAOP (mm Hg)	7 (2)	8 (2)	8 (3)	0.583
Cardiac index (litre min^{-1} m^{-2})	2.83 (0.68)	2.98 (0.63)	3.17 (0.57)*	0.047
Blood flow index (litre min^{-1} m^{-2})				
Splanchnic	0.69 (0.22)	0.68 (0.24)	0.64 (0.14)	0.433
Femoral	0.18 (0.07)	0.23 (0.09)†	0.20 (0.05)	<0.001
Vascular resistance index (dyn s cm^{-5} m^{-2})				
Systemic	2560 (850)	2100 (500)*	1880 (380)*	0.001
Splanchnic	11 500 (4350)	10530 (3230)	10 430 (3550)	0.350
Femoral	44 180 (14 010)	30 850 (9740)#	31870 (8530)#	0.009
$V\text{O}_2$ index (ml min^{-1} m^{-2})				
Systemic	126 (18)	133 (16)*	135 (14)*	0.012
Splanchnic	40 (6)	42 (8)	42 (7)	0.238
Femoral	10 (2)	10 (3)	9 (2)	0.514
$V\text{CO}_2$ index (ml min^{-1} m^{-2})				
Systemic	97 (16)	103 (15)*	104 (11)*	0.019
Splanchnic	27 (5)	29 (9)	27 (5)	0.222
Femoral	9 (2)	10 (3)	8 (2)	0.124
Oxygen extraction				
Systemic	0.31 (0.05)	0.32 (0.05)	0.32 (0.06)	0.696
Splanchnic	0.43 (0.15)	0.47 (0.14)	0.50 (0.12)*	0.018
Femoral	0.41 (0.13)	0.33 (0.13)*	0.34 (0.10)	0.020
Blood temperature (°C)	37.6 (0.6)	33.2 (0.5)†	38.3 (0.5)†	<0.001
Haemoglobin (g litre^{-1})	109 (13)	102 (9)†	101 (9)*	0.003

Table 3. Parameters of local and regional metabolism ($n=17$; for lactate and pyruvate, $n=15$). Reference values for venous–arterial $P\text{CO}_2$ gradients from 43 preoperative abdominal surgery patients;[27] sources of other reference values are given in Methods Values are mean (SD). *P*: time effect, multiple analysis of variance for repeated measurements. $^*P<0.05$, $^†P<0.01$ *vs* ICU admission, Wilcoxon signed ranks sum test

	Reference	ICU admission	3 h	6 h	*P*
$P\text{CO}_2$ gradient (kPa)					
Mixed venous–arterial	0.64 (0.15)	0.72 (0.14)	0.82 (0.11)*	0.83 (0.16)*	0.011
Hepatic venous–arterial	0.52 (0.21)	0.45 (0.18)	0.48 (0.13)	0.58 (0.22)†	0.019
Femoral venous–arterial	0.59 (0.28)	1.09 (0.29)	0.98 (0.34)	0.97 (0.30)	0.341
Mucosal–arterial	1.36 (0.96)	1.26 (1.26)	1.19 (0.86)	1.46 (0.66)	0.822
Lactate (mmol litre^{-1})					
Arterial	1.1 (0.4)	1.1 (0.3)	1.2 (0.3)*	1.2 (0.3)*	0.017
Hepatic		0.6 (0.2)	0.7 (0.3)	0.7 (0.3)	0.277
Femoral		1.4 (0.3)	1.5 (0.3)	1.5 (0.4)	0.152
Pyruvate (µmol litre^{-1})					
Arterial	99 (29)	81 (21)	91 (23)	117 (46)†	0.003
Hepatic		52 (26)	71 (38)*	84 (53)	0.034
Femoral		84 (28)	99 (26)*	108 (32)†	0.002
L/P ratio					
Arterial	11 (2)	14 (2)	14 (3)	12 (1)†	<0.001
Hepatic		18 (15)	11 (3)*	11 (4)	0.047
Femoral		17 (2)	16 (3)	15 (3)	0.064
GSTA (µg litre^{-1})					
Arterial	4.3 (2.8)	15 (13)	6.3 (5.9)†	4.2 (3.4)†	<0.001
Hepatic		18 (14)	10 (15)†	5.6 (4.2)†	0.003

femoral oxygen consumption, systemic blood flow was redistributed to peripheral tissues. (ii) Although splanchnic oxygen extraction was high, we found no evidence of impaired liver function or cellular integrity. (ii) The adequacy of blood flow could not be assessed from changes in systemic and regional venous–arterial $P\text{CO}_2$ gradients.

Increasing metabolic activity and a preferential increase in peripheral perfusion may account for the increase in splanchnic oxygen extraction. In certain patients, splanchnic oxygen extraction was in the range where organ dysfunction or damage is likely to occur.[19,20] Even under these conditions, subsequent weaning from the ventilator had very little effect, and the oxygen transport to splanchnic tissue did not deteriorate further. Metabolic needs increase after cardiopulmonary bypass.[6,10] Compromised cardiac function, resulting from either pre-existing cardiac disease or post-operative myocardial dysfunction,[21] may limit the increase in systemic blood flow, so redistribution of flow to regions with increasing oxygen demands is likely to occur. Though we could not determine where oxygen consumption

Table 4 Haemodynamics and oxygen transport variables ($n=11$) and mucosal–arterial $P\text{CO}_2$ gradients ($n=10$) before and after extubation (mean (SD))

	Before extubation	**After extubation**	***P***
Cardiac index (litres $\text{min}^{-1}\ \text{m}^{-2}$)	3.13 (0.60)	3.24 (0.57)	0.131
Blood flow index (litres $\text{min}^{-1}\ \text{m}^{-2}$)			
Splanchnic	0.63 (0.14)	0.73 (0.25)	0.110
Femoral	0.23 (0.05)	0.20 (0.04)	0.016
Vascular resistance index (dyn s $\text{cm}^{-5}\ \text{m}^{-2}$)			
Systemic	1970 (330)	1850 (320)	0.114
Splanchnic	10 800 (3380)	9820 (2100)	0.214
Femoral	28 940 (5640)	33 760 (8860)	0.047
$V\text{O}_2$ index (ml $\text{min}^{-1}\ \text{m}^{-2}$)			
Systemic	131 (24)	136 (20)	0.374
Splanchnic	42 (7)	45 (8)	0.374
Femoral	9 (2)	10 (2)	0.248
Oxygen extraction			
Systemic	0.32 (0.05)	0.39 (0.10)	0.062
Splanchnic	0.48 (0.08)	0.43 (0.09)	0.062
Femoral	0.30 (0.09)	0.34 (0.07)	0.075
Gastric mucosal–arterial $P\text{CO}_2$ gradient (kPa)	0.90 (1.08)	0.80 (1.18)	0.500

increased, the brain (recovery from anaesthesia), respiratory muscles (weaning from mechanical ventilation) and skin (rewarming) may all have contributed.

Despite high and increasing splanchnic oxygen extraction, blood flow was also redistributed to the leg, where oxygen extraction was low, and oxygen consumption was stable and low. Thermoregulatory effects may have played a role: increasing peripheral temperature after cardiopulmonary bypass can be achieved by locally increasing either metabolism[22] or blood flow. During rewarming, skeletal muscle oxygen demand may increase substantially because of shivering. There was no shivering in the study patients. Furthermore, since oxygen consumption in the leg did not change, an increase in skeletal muscle oxygen demand is very unlikely. Vasoregulation, aimed to achieve passive rewarming of the extremities, may have favoured femoral rather than splanchnic blood flow. Another explanation is disturbed vasoregulation after peripheral vasoconstriction and ischaemia during cardiopulmonary bypass (reperfusion). The high L/P ratios in femoral venous blood after ICU admission support this hypothesis. Finally, it is posssible that increased femoral blood flow and splanchnic oxygen extraction occur in parallel in these patients, rather than being coupled phenomena.

The high splanchnic oxygen extraction, exceeding 0.75 in some patients, suggests that organ dysfunction may arise. Despite the marginal perfusion of the splanchnic organs, we found no evidence of organ dysfunction. Liver function, as assessed by indocyanine green extraction, was normal. Individual high splanchnic L/P ratios (up to 65) at ICU admission resulted from low pyruvate rather than high lactate concentrations, and are therefore unlikely to indicate anaerobic metabolism.[23] As a result of the high lactate extraction capability of the liver, only excessive anaerobic mesenteric metabolism or frank liver hypoxia will result in systemic hyperlactataemia. It is likely that the observed increase in splanchnic oxygen extraction was sufficient to compensate for the lack of increase in blood flow and to maintain aerobic metabolism in the splanchnic region.

The only sign of subclinical organ damage was the increased concentration of GSTA at ICU admission. The increase in the arterial GSTA concentration was slightly higher than that during halothane or isoflurane anaesthesia but far lower than that during postoperative bleeding.[18] It is possible that halothane was causally involved in the release of GSTA, but this seems unlikely because it was used only during brief episodes and the first GSTA measurements were taken several hours after that. Increased GSTA release and decreased elimination can both result in increased GSTA blood concentrations. Because the half-life of GSTA is short,[17] increased release seems more likely. The subsequent decrease in both arterial and liver vein GSTA concentration indicate that the disturbance of the integrity in GSTA-producing cells during cardiopulmonary bypass subsequently resolved. GSTA-producing cells are mainly hepatocytes, renal tubular and small intestine epithelial cells.[24] Though the mean GSTA concentrations in arterial blood were lower than those in hepatic venous blood, the differences were usually small, and in four patients the arterial concentration was higher than the liver venous concentration at least during one measurement period. This suggests that the liver may take up GSTA, and may not necessarily be the main origin of GSTA production in individual patients. Possibly, renal tubular cells release a substantial amount of GSTA, since subclinical renal damage may occur after cardiopulmonary bypass.[25] Weaning from the ventilator did not lead to any deterioration in liver function or cellular integrity.

It has been suggested that venous–arterial $P\text{CO}_2$ gradients are useful variables in the monitoring of perfusion.[26 27] In this study, neither systemic nor regional venous–arterial $P\text{CO}_2$ gradients reflected changes in blood flow (Fig. 1A). Flow changes will affect venous–arterial carbon dioxide content differences. Under stable conditions the relation between carbon dioxide content and $P\text{CO}_2$ is almost linear. This is not the case if haemoglobin, pH, the absolute values of arterial and venous $P\text{CO}_2$ or oxygen saturation change. The latter is known as the Haldane effect: increasing oxygen saturation will increase the $P\text{CO}_2$ for any given carbon dioxide content. Figure 1B shows the inconsistent relationship between changes in splanchnic venous–arterial carbon dioxide content and venous–arterial $P\text{CO}_2$ gradients. The measured shifts in pH, haemoglobin, arterial and venous P_{CO_2} and, most importantly, venous oxygen saturation in the postoperative period explain these findings. Since we did not measure gastric mucosal oxygen saturation, mucosal arterial carbon dioxide content could not be calculated. Nevertheless, changes in tissue oxygen extraction will also affect gastric mucosal–arterial $P\text{CO}_2$ gradients. In individual patients, increasing mucosal–arterial $P\text{CO}_2$ gradients do not

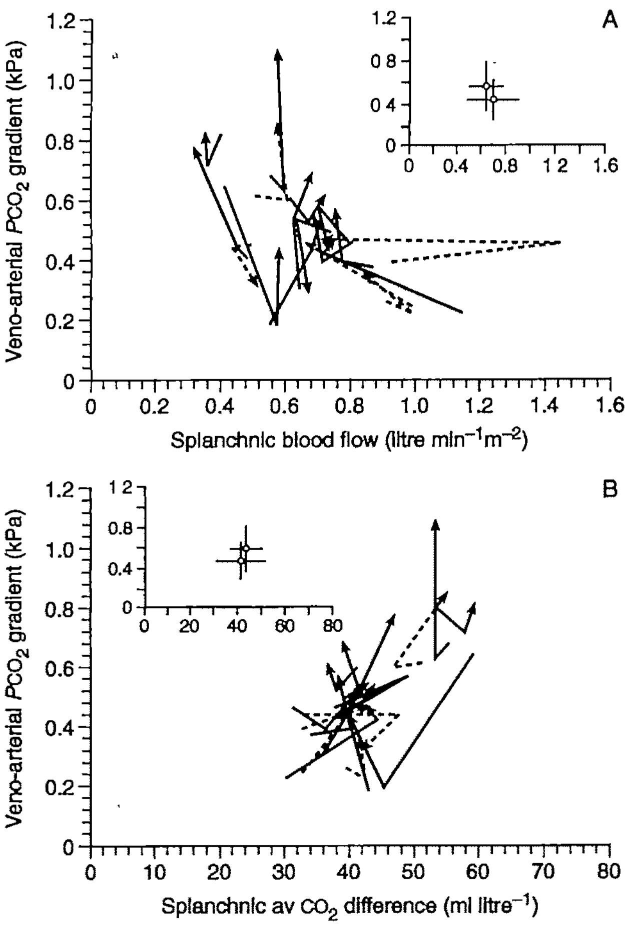

Fig 1 Relation between liver venous–arterial Pco_2 gradients and splanchnic blood flow (A), and arteriovenous carbon dioxide content (B). Three measurements for each patient are shown. Triangles mark the last measurement. Dashed lines: patients who received sodium nitroprusside. The insets indicate group mean (SD) from the first and the third measurements

necessarily reflect an inadequate blood flow in relation to the carbon dioxide production.

Extubation was associated with redistribution of systemic blood flow: femoral blood flow decreased while global and local splanchnic perfusion was maintained. Blood flow may have been redirected to the respiratory muscles. It has been shown that splanchnic ischaemia, defined as low gastric mucosal pH, is a good predictor of weaning failure.[11 28] Weaning from the ventilator did not fail in any of our patients, even though splanchnic perfusion was marginal in some of them. However, the patients had been on the ventilator for a short time only, and their preoperative lung function was normal, which may explain the discrepancies.

We conclude that the predominant increase in peripheral blood flow, despite unchanged oxygen demands–caused either by thermoregulation or by disturbed vasoregulation after ischaemia–together with increased oxygen uptake in certain regions of the body increase the risk of a mismatch between splanchnic perfusion and metabolic demands. Postoperative changes in oxygen extraction, pH and haemodilution alter the relation between Pco_2 and carbon dioxide content, and explain why systemic and regional venous–arterial Pco_2 gradients do not necessarily reflect the adequacy of blood flow in individual patients. We suggest that high splanchnic oxygen extraction and restored femoral vasoregulation are the most likely reasons for an opposite redistribution of blood flow–away from the femoral region–after extubation. The overall relatively moderate changes in oxygen transport variables and the uncomplicated clinical course should be interpreted in the context of the selected patients, who had stable cardiac function and no clinical signs of heart failure.

Appendix

Calculation of the veno-arterial carbon dioxide content

Veno-arterial carbon dioxide content was measured using the method developed by Giovannini and colleagues.[14] Briefly, arterial carbon dioxide content is determined from the content of combined carbon dioxide in plasma ($Ca_{CO_2}p$) and red blood cells ($Ca_{CO_2}r$), dissolved carbon dioxide and haematocrit. $Ca_{CO_2}p$ is calculated from arterial carbon dioxide tension and plasma pH (pH_a) by using the Henderson–Hasselbalch equation. The ratio between $Ca_{CO_2}r$ and $Ca_{CO_2}p$ is a function of plasma pH and arterial oxygen saturation (Sa_{O_2}). The increase in blood carbon dioxide content resulting from an increase in carbon dioxide tension and from the simultaneous decrease in Sa_{O_2}, which occurs when arterial blood becomes venous, is calculated by taking these two components into account separately, and by using the mathematical model developed and described in detail by Giovannini and colleagues.[14] This model simulates the equilibration of whole blood at increasing carbon dioxide tensions to determine the virtual values of combined carbon dioxide content in plasma and of plasma pH, resulting from the increase in carbon dioxide tension from arterial to venous value at constant Sa_{O_2}. In a further step the increment in blood carbon dioxide content that is related to the decrease in oxygen saturation from arterial to venous value at constant carbon dioxide tension is then calculated. The total increment in carbon dioxide content from arterial to venous blood is finally calculated from the sum of both changes. The venous arterial carbon dioxide content calculated using this model compared well with and did not differ significantly from results of 26 previously published measurements (references cited in reference 14).

Comparison between measured and calculated oxygen consumption (Vo_2) and carbon dioxide production (Vco_2)

In the total of 51 measurements, systemic oxygen consumption–as measured by indirect calorimetry–was significantly higher than Vo_2Fick ($P<0.01$), whereas Vco_2 calculated

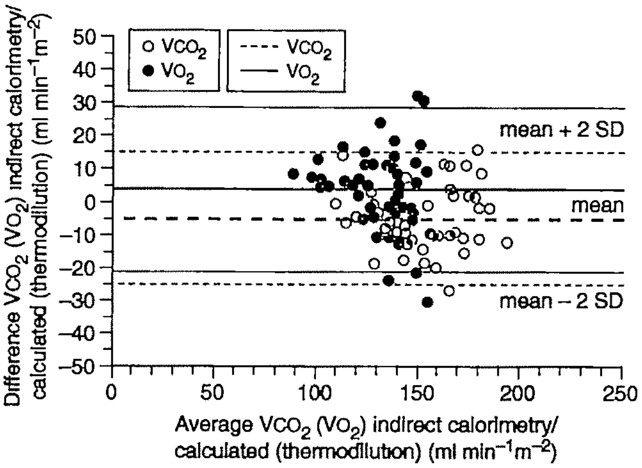

Fig 2 Bland–Altman diagram for comparison of $V\mathrm{co}_2$ ($V\mathrm{o}_2$) obtained by two different methods (pooled data; see Appendix for further explanation)

was higher than $V\mathrm{co}_2$ measured by indirect calorimetry (P=0.006). The mean (SD) difference between the two methods was small: –4.35 (10.0) ml min^{-1} m^{-2} ($V\mathrm{o}_2$), and 4.27 (12.5) ml min^{-1} m^{-2} ($V\mathrm{co}_2$), but significantly different from zero (confidence interval –7.4 to –1.3 ml min^{-1} m^{-2} ($V\mathrm{o}_2$); 0.6–7.9 ml min^{-1} m^{-2} ($V\mathrm{co}_2$)). Despite the difference, $V\mathrm{o}_2$Fick ($V\mathrm{co}_2$ calculated) and $V\mathrm{o}_2$ ($V\mathrm{co}_2$) measured by indirect calorimetry correlated well [r^2=0.75, P<0.01 ($V\mathrm{o}_2$); r^2=0.82, P<0.01 ($V\mathrm{co}_2$)]. A good agreement between the two methods is also demonstrated in the Bland–Altman graph[29] (Fig. 2).

References

1 Craddock D, Iyer VS, Russell WJ. Factors influencing mortality and myocardial infarction after coronary artery bypass grafting. *Curr Opin Cardiol* 1994; **9:** 664–9

2 Mills SA. Cerebral injury and cardiac operations. *Ann Thorac Surg* 1993; **56** (Suppl.): 86–91

3 Mythen MG, Webb AR. Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost. *Intensive Care Med* 1994; **20:** 99–104

4 Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Arch Surg* 1995; **130:** 423–9

5 Landow L, Phillips DA, Heard SO *et al.* Gastric tonometry and venous oximetry in cardiac surgery patients. *Crit Care Med* 1991; **19:** 1226–33

6 Parviainen I, Ruokonen E, Takala J. Dobutamine-induced dissociation between changes in splanchnic blood flow and gastric intramucosal pH after cardiac surgery. *Br J Anaesth* 1995; **74:** 277–82

7 Uusaro A, Ruokonen E, Takala J. Splanchnic oxygen transport after cardiac surgery: evidence for inadequate tissue perfusion after stabilization of haemodynamics. *Intensive Care Med* 1996; **22:** 26–33

8 Sicsic JC, Duranteau J, Corbineau H *et al.* Gastric mucosal oxygen delivery decreases during cardiopulmonary bypass despite constant systemic oxygen delivery. *Anesth Analg* 1998; **86:** 455–60

9 Parviainen I, Rantala A, Ruokonen E, Tenhunen J, Takala J. Angiotensin converting enzyme inhibition has no effect on blood pressure and splanchnic perfusion after cardiac surgery. *J Crit Care* 1998; **13:** 73–80

10 Uusaro A, Ruokonen E, Takala J. Gastric mucosal pH does not reflect changes in splanchnic blood flow after cardiac surgery. *Br J Anaesth* 1995; **74:** 149–54

11 Bouachour G, Guiraud MP, Gouello JP *et al.* Gastric intramucosal pH: an indicator of weaning outcome from mechanical ventilation in COPD patients. *Eur Respir J* 1996; **9:** 1868–73

12 Ramsay MAE, Savege TM, Simpson BJ *et al.* Controlled sedation with alphaxalone/alphadalone. *Brit Med J* 1974; **2:** 656–9

13 Uusaro A, Ruokonen E, Takala J. Estimation of splanchnic blood flow by the Fick principle in man and problems in the use of indocyanine green. *Cardiovasc Res* 1995; **30:** 106–12

14 Giovannini I, Chiarla C, Boldrini G, Castagneto M. Calculation of venoarterial CO_2 content. *J Appl Physiol* 1993; **74:** 959–64

15 Parviainen I, Vaisanen O, Ruokonen E, Takala J. Effect of nasogastric suction and ranitidine on the calculated gastric intramucosal pH. *Intensive Care Med* 1996; **22:** 319–23

16 Solberg HE. International Federation of Clinical Chemistry (IFCC), Scientific Committee, Clinical Section, Expert Panel on Theory of Reference Values, and International Committee for Standardization in Hematology (ICSH), Standing Committee on Reference Values. Approved Recommendation (1986) on the theory of reference values. Part 1. The concept of reference values. *J Clin Chem Clin Biochem* 1987; **25:** 337–42

17 Tiainen P. Hepatocellular integrity in liver donors and recipients indicated by glutathione transferase alpha. *Transplantation* 1996; **61:** 904–8

18 Tiainen P. Hepatocellular integrity during and after isoflurane and halothane anaesthesia in surgical patients. *Br J Anaesth* 1996; **77:** 744–7

19 Rowell LB, Blackmon JR, Kenny MA, Escourrou P. Splanchnic vasomotor and metabolic adjustments to hypoxia and exercise in humans. *Am J Physiol* 1984; **247:** H251–8

20 Nelson DP, Samsel RW, Wood LDH, Schumacker PT. Pathological supply dependence on systemic and intestinal O_2 uptake during endotoxemia. *J Appl Physiol* 1988; **64:** 2410–9

21 Vinten-Johansen J, Nakanishi KJ. Postcardioplegia acute cardiac dysfunction and reperfusion injury. *Cardiothorac Vasc Anesth* 1993, **7** (Suppl.): 6–18

22 Licker M, Schweizer A, Ralley FE. Thermoregulatory and metabolic responses following cardiac surgery. *Eur J Anaesthesiol* 1996; **13:** 502–10

23 Huckabee WE. Relationships of pyruvate and lactate during anaerobic metabolism. I. Effects of infusion of pyruvate or glucose and of hyperventilation *J Clin Invest* 1958; **37:** 244–54

24 Campbell JAH, Corrigall AV, Guy A, Kirsch RE. Immunhistologic localization of alpha, mu, and pi class glutathione S-transferases in human tissues. *Cancer* 1991; **67:** 1608–13

25 Mazzarella V, Gallucci MT, Tozzo C *et al.* Renal function in patients undergoing cardiopulmonary bypass operations. *J Thorac Cardiovasc Surg* 1992; **104:** 1625–7

26 Teboul JL, Graini L, Boujdaria R *et al.* Cardiac index vs oxygen-derived parameters for rational use of dobutamine in patients with congestive heart failure. *Chest* 1993; **103:** 81–5

27 Ruokonen E, Soini HO, Parviainen I *et al.* Venoarterial CO_2 gradient after cardiac surgery: relation to systemic and regional perfusion and oxygen transport. *Shock* 1997; **8:** 335–40

28 Mohsenifar Z, Collier J, Koerner SK. Gastric intramural pH in mechanically ventilated patients. *Thorax* 1996; **51:** 606–10

29 Bland JM, Altman DG Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **i:** 307–10

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Myocardial consequences of remifentanil in patients with coronary artery disease

S. Kazmaier[1], G.-G. Hanekop[1], W. Buhre[1], A. Weyland[1], T. Busch[2], O. C. Radke, R. Zoelffel[1] and H. Sonntag[1]

[1]Department of Anaesthesiology, Emergency and Intensive Care Medicine and [2]Department of Thoracic, Cardiovascular and Vascular Surgery, Georg August University of Göttingen, Göttingen, Germany

**Corresponding author: Zentrum Anaesthesiologie, Rettungs- und Intensivmedizin, Georg-August-Universität Göttingen, Robert-Koch-Strasse 40, D-37075 Göttingen, Germany*

Remifentanil may be an alternative to conventional opioids for minimally invasive direct coronary artery bypass surgery because of its extremely short duration of action. The aim of this study was to investigate the effects of remifentanil on myocardial blood flow, metabolism and systemic haemodynamic variables in patients with coronary artery disease. After approval by the local ethics committee, 12 male patients were investigated before elective coronary artery bypass grafting. Systemic haemodynamic variables, myocardial blood flow and metabolism were measured when patients were awake and when they were anaesthetized with high-dose remifentanil (2.0 μg kg^{-1} min^{-1}), or with remifentanil 0.5 μg kg^{-1} min^{-1} combined with propofol (target-controlled infusion aiming at a plasma concentration of 2.0 μg ml^{-1}). Myocardial blood flow was measured using a modified Kety–Schmidt technique. High-dose remifentanil anaesthesia significantly reduced cardiac index (CI) (–25%) as a consequence of a decrease in stroke volume index (SVI) (−14%) and heart rate (−13%). Mean arterial pressure (MAP) was 30% lower than that in the awake patient. Myocardial blood flow and myocardial oxygen uptake (MVo_2) decreased by 30% and 42%, respectively. In contrast to high-dose remifentanil anaesthesia, systemic vascular resistance index (−14%) during remifentanil/propofol anaesthesia was significantly lower than that in the awake patient. Other haemodynamic variables, and myocardial blood flow and MVo_2, did not significantly differ from the high-dose remifentanil period. In conclusion, high-dose remifentanil reduces SVI, heart rate, MAP, myocardial blood flow and MVo_2 and its effects do not differ from those of remifentanil/propofol anaesthesia.

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In addition to causing loss of consciousness and analgesia, anaesthesia for coronary artery bypass grafting (CABG) has to provide haemodynamic stability, maintain integrity of myocardial function and minimize sympathetic response to surgical stimuli. Anaesthesia, therefore, is often performed using high-dose opioids combined with benzodiazepines. In addition to the consequences of hypothermic cardiopulmonary bypass, the long duration of action of the applied opioids may also contribute to the need for postoperative ventilatory support. The development of new minimally invasive techniques allows cardiac surgical intervention without using hypothermic cardiopulmonary bypass.[1] Early extubation at the end of surgery seems to be practicable in patients with uncomplicated intraoperative course.[2] In these cases, the use of short-acting anaesthetic drugs may be advantageous.

Remifentanil is a new, short-acting opioid with a context-sensitive half-time of about 3.0 min.[3] It is metabolized by non-specific plasma and tissue esterases[4] and its elimination is, therefore, independent of hepatic and renal function.[5] Remifentanil has metabolites with minimal intrinsic activity.

Initial studies[6 7] investigating remifentanil for cardiac anaesthesia did not find any differences in systemic haemodynamic responses, time of rewarming, blood loss and pulmonary gas exchange in the postoperative period when compared with fentanyl. However, in patients treated with remifentanil, the trachea could be extubated significantly earlier. Little information is available about the effects of remifentanil on myocardial blood flow and metabolism. The aim of this prospective clinical study was to investigate in detail the effects of high-dose remifentanil anaesthesia and remifentanil/propofol anaesthesia on systemic haemo-

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Table 1. Patient characteristics Ate, atenolol, Aml, amlodipin; Bis, bisoprolol, Cap, captopril; Cel, celiprolol; Dil, diltiazem, Ena, enalapril; Fel, felodipin, Hyd, hydrochlorthiazide, Iso, isosorbide dinitrate, Ism, isosorbide mononitrate, Lis, lisinopril, Met, metoprolol, Mg, magnesium, Mib, mibefradil, Mol, molsidomin, Mox, moxonidin, Pen, pentaerithryltetranitrate, Ram, ramipril, Sot, sotalol, LAD, left anterior descending coronary artery; Cx, circumflex coronary artery, RCA, right coronary artery

No.	Hypertension	History of MI	NYHA classification	Cardiovascular medication	Location of coronary artery disease
1	+	−	I	Ate, Ism	LAD, Cx, RCA
2	+	−	III	Aml, Mg, Sot	LAD, Cx, RCA
3	+	+	II	Iso, Lis, Met, Mol	LAD, Cx, RCA
4	+	−	II	Mib	LAD, Cx, RCA
5	+	−	II	Cel, Mol, Ram	LAD, Cx, RCA
6	+	−	II	Fel, Hyd, Iso,	LAD, Cx, RCA
7	−	+	II	Ate, Cap, Iso, Mol	LAD, Cx
8	+	−	III	Dil, Ena	LAD, Cx, RCA
9	+	+	II	Ate, Iso, Mol	LAD, Cx, RCA
10	−	−	II	Lis, Pen	LAD, Cx, RCA
11	+	+	I	Cap, Iso, Mol, Mox	LAD, Cx, RCA
12	+	+	III	Bis, Cap	LAD, RCA

dynamic variables, myocardial blood flow and myocardial metabolism in patients with coronary artery disease.

Methods

The study was approved by the local institutional review committee and written informed consent was obtained from each patient.

Patients

Twelve male patients (mean (SD) age 61 (range 52–69) yr, weight 91 (12) kg, height 175 (9) cm, body surface area 2.1 (0.2) m^2) with coronary artery disease were investigated before elective CABG surgery. Individual patients' characteristics, location of coronary artery disease and long-term medication are given in Table 1. Patients with preoperative evidence of a stenosis of the left main coronary artery, valvular heart disease, impaired left ventricular function (ejection fraction <40%), neurological disorders, increased plasma concentrations of transaminases or creatinine, or coagulopathy were excluded from the study. Antiarrhythmic and antihypertensive medications were continued until the day of surgery. Premedication consisted of flunitrazepam 2 mg orally on the evening before surgery, and the next morning before the beginning of the study period.

Catheterization

After arrival in the theatre, ECG leads were attached and continuous ST-segment analysis of lead II and V$_5$ (60 ms after *j*-point; Sirecust 1281; Siemens, Erlangen, Germany) was initiated. A 20-gauge catheter was placed in the radial artery for measurement of mean arterial pressure (MAP). Subsequently, the following catheters were inserted: (i) a flow-directed pulmonary artery catheter (ARROW Hands-off thermodilution catheter AH-05000) via the left internal jugular vein for measurement of central venous pressure (CVP), mean pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and cardiac output; (ii) a Goodale–Lubin catheter (7.0 F, USCI) via the right internal jugular vein into the coronary sinus for measurement of coronary sinus pressure and coronary sinus blood sampling; (iii) a second Goodale–Lubin catheter, of identical diameter and length, via the left femoral artery in the descending aorta. The Goodale–Lubin catheters, which were used to measure myocardial blood flow, exhibit only minimal loss of gas by diffusion. The positioning of both Goodale–Lubin catheters and of the pulmonary artery catheter was verified by fluoroscopy. Body temperature was kept constant using convective air warming.

Clinical protocol and measurements

The first measurement was performed in the awake patient. Anaesthesia was then induced with remifentanil 1.0 μg kg^{-1}, etomidate 0.2 mg kg^{-1}. Tracheal intubation was facilitated with pancuronium bromide 0.1 mg kg^{-1}. After tracheal intubation, the lungs were ventilated by a volume-controlled respirator (AV 1; Dräger, Germany) with a $F_{I_{O_2}}$ of 0.3. Arterial blood gas analyses (ABL 500; Radiometer, Copenhagen, Denmark) and continuous end-expiratory carbon dioxide measurements (Capnomac Ultima; Datex, Helsinki, Finland) were performed to verify normoventilation (arterial P_{CO_2} 5.3 (0.3) kPa). A second measurement was performed under anaesthesia with remifentanil 2.0 μg kg^{-1} min^{-1} and a third measurement under anaesthesia with remifentanil 0.5 μg kg^{-1} min^{-1} combined with a target-controlled infusion of propofol aiming at a plasma concentration of 2.0 μg ml^{-1}. A resting period of at least 30 min before each measurement was part of the study protocol to ensure steady state conditions.

At the beginning of each measurement period, heart rate, MAP, CVP, coronary sinus pressure, PAP and PCWP were recorded (Sirecust 1281, Siredoc 220; Siemens, Erlangen, Germany). Cardiac output was assessed by thermodilution as the mean of three injections of 10 ml ice-cooled isotonic saline solution randomly spread over the respiratory cycle. Arterial and coronary sinus blood samples were drawn in duplicate immediately before and after each period of myocardial blood flow measurement for determination of pH (pH_{art}, pH_{cs}), blood gas tensions (Pa_{O_2}, Pcs_{O_2}, Pa_{CO_2}, Pcs_{CO_2}), oxygen saturation (Sa_{O_2}, Scs_{O_2}), haemoglobin (CO Oximeter IL 282; Woodstock, NY, USA), glucose, lactate (standard test kits; Boehringer, Mannheim, Germany) and electrolyte concentrations (NOVA CRT 1, Waltham, MA, USA). The mean of the two samples was calculated and used for further analysis. Additional arterial blood samples were withdrawn in duplicate for determination of epinephrine and norepinephrine plasma levels (HPLC with fluorescence detection; coefficient of variation 3.8%). Myocardial blood flow was measured by a modified Kety–Schmidt technique using argon as the tracer[8 9] (coefficient of variation 5.1%). A pre-prepared gas mixture containing 70% argon and 30% oxygen was administered to the awake patient via a tightly fitting mouthpiece and to the anaesthetized patient via the tracheal tube. Blood samples from the arterial and the coronary sinus catheter were withdrawn into glass syringes at a constant rate during the saturation period in duplicate by use of a high-precision aspiration pump (modified Unita I; Braun, Melsungen, Germany). Argon wash-in periods of 5 min were used for all measurements. Triple determinations of argon concentrations in each arterial and coronary venous blood sample were carried out after vacuum extraction by gas chromatography and β-ionization detection. An argon myocardium/blood partition coefficient of 1.1 was used for calculation of myocardial blood flow.

Calculations

Cardiac index (CI), stroke volume index (SVI), systemic and pulmonary vascular resistance indices (SVRI and PVRI), arterial and coronary sinus oxygen content (Ca_{O_2} and Ccs_{O_2}) were calculated according to standard formulae. Myocardial uptake of oxygen (MV_{O_2}) and glucose were calculated as the product of the respective arterial–coronary sinus content differences and myocardial blood flow. Myocardial lactate extraction was calculated as the ratio between the arterial–coronary sinus content difference and arterial lactate content. Coronary perfusion pressure was calculated as the difference between mean diastolic pressure and PCWP, and coronary vascular resistance was calculated as the ratio between coronary perfusion pressure and myocardial blood flow.

Statistics

Results are expressed as mean (SD). Parametric statistical analysis was performed by one-way analysis of variance using a repeated measures design. Scheffe's test was used for two-tailed *post hoc* comparison of data if appropriate. $P<0.05$ was considered significant. All statistical procedures were performed on a microcomputer with the STATISTICA software package (Statsoft Inc., release 4.5).

Results

Haemodynamic data and the results of arterial and coronary sinus blood gas analyses are given in Table 2.

High-dose remifentanil reduced MAP by 30% ($P<0.05$) compared with the awake period. This resulted primarily from a 25% decrease in CI ($P<0.05$), which was accompanied by a concomitant decrease in SVI and heart rate by 14% ($P<0.05$) and 13% ($P<0.05$), respectively. CVP was 26% greater than in awake patients ($P<0.05$) but PCWP did not change. There was no significant change in SVRI, PVRI or PAP.

Maintaining anaesthesia with remifentanil and propofol reduced MAP and PAP by 37% ($P<0.05$) and 12% ($P<0.05$), respectively, compared with the awake period. During this period the decrease in MAP was caused mainly by a decrease in CI and SVRI by 24% and 25%, respectively (both $P<0.05$). The decrease in CI was caused by a 19% decrease in heart rate ($P<0.05$); SVI was not significantly different from that in awake patients. Similarly to the high-dose remifentanil period, CVP was 26% higher ($P<0.05$) and PVRI and PCWP remained unchanged. No significant differences were found for all investigated haemodynamic variables between high-dose remifentanil and remifentanil/propofol anaesthesia.

Maintaining anaesthesia with high-dose remifentanil and remifentanil/propofol reduced the plasma concentration of epinephrine by 56% and 63%, respectively (both $P<0.05$), and reduced the plasma concentration of norepinephrine by 47% and 66%, respectively (both $P<0.05$) compared with the awake period.

Mean values of myocardial blood flow, coronary perfusion pressure, coronary vascular resistance and myocardial metabolic variables are given in Table 3. High-dose remifentanil reduced coronary perfusion pressure by 32% ($P<0.05$) compared with the awake period. Myocardial blood flow decreased by 30% ($P<0.05$) whereas coronary vascular resistance did not change significantly. The reduction of myocardial blood flow was accompanied by a decrease in MV_{O_2} and myocardial glucose uptake by 42% ($P<0.05$) and 59% ($P<0.05$), respectively. This resulted in a decrease in the arterial coronary sinus oxygen content difference ($acsD_{O_2}$) by 19% ($P<0.05$), indicating reduced myocardial oxygen extraction.

During remifentanil/propofol anaesthesia, coronary perfusion pressure decreased by 40% ($P<0.05$) compared with that in awake patients. During this measurement period, the decrease in myocardial blood flow by 25% ($P<0.05$) was associated with a reduction in coronary vascular resistance by 29% ($P<0.05$). MV_{O_2} and $acsD_{O_2}$ decreased by 44% ($P<0.05$) and 25% ($P<0.05$), respectively. $AcsD_{O_2}$ decreased more than in the high-dose remifentanil period, indicating a further decrease in myocardial oxygen extraction. During remifentanil/propofol anaesthesia, the decrease in myocardial uptake of glucose (72% of the awake state) was not significantly different from that during high-dose remifentanil anaesthesia ($P<0.05$).

No signs of ischaemia were detected in any of the patients throughout the study period: myocardial lactate extraction did not reach negative values greater than –5% and continu-

Table 2. Mean (SD) of global haemodynamic variables, blood gas analyses and body temperature MAP, mean arterial pressure, CVD, central venous pressure, PAP, mean pulmonary artery pressure, PCWP, pulmonary capillary wedge pressure, SVRI, systemic vascular resistance index, PVRI, pulmonal vascular resistance index, Sa_{O_2} and Scs_{O_2}, arterial and coronary sinus oxygen saturation, Pa_{O_2}, arterial oxygen partial pressure; Pa_{CO_2}, arterial carbon dioxide partial pressure, $T_{bladder}$, body temperature, measured in the urinary bladder $^*P<0$ 05 compared with awake, $^\dagger P<0$ 05 remifentanil/propofol compared with remifentanil

	Awake	**Remifentanil**	**Remifentanil/propofol**
Cardiac index (litres $min^{-1}m^{-2}$)	3.2 (0.7)	2 4 (0.4)*	2 4 (0 4)*
Stroke volume index (ml m^{-2})	47 (9)	40 (8)*	43 (6)
Heart rate (beats min^{-1})	69 (14)	60 (10)*	56 (9)*
MAP (mm Hg)	109 (13)	76 (9)*	68 (6)*
CVP (mm Hg)	8 (2)	9 (2)*	9 (2)*
PAP (mm Hg)	20 (4)	18 (3)	18 (3)*
PCWP (mm Hg)	10 (3)	11 (2)	11 (3)
SVRI (dyn s cm^{-5} m^2)	2650 (593)	2315 (470)	1997 (380)*
PVRI (dyn s cm^{-5} m^2)	268 (90)	264 (84)	231 (59)
Sa_{O_2} (%)	97 (1)	97 (2)	98 (1)†
Scs_{O_2} (%)	30 (6)	35 (4)*	36 (3)*
Pa_{O_2} (kPa)	12.8 (1.8)	12 9 (3.3)	13.9 (3 1)
Pa_{CO_2} (kPa)	5 4 (0 4)	5.2 (0.4)	5 0 (0 4)
Arterial pH	7 42 (0 03)	7.42 (0.05)	7 44 (0 05)
$[Na^+]$ (mmol $litre^{-1}$)	140 (3)	141 (2)	141 (3)
$[K^+]$ (mmol $litre^{-1}$)	4.3 (0.8)	4 3 (0.7)	4.2 (0 6)
$T_{bladder}$ (°C)	36 5 (0.4)	36 4 (0.4)	36 4 (0 5)

Table 3. Mean (SD) of catecholamine concentrations, myocardial haemodynamic and metabolic variables. CPP, coronary perfusion pressure, CVR, coronary vascular resistance; myocardial blood flow, myocardial blood flow; $acsDO_2$, arterial coronary sinus oxygen content difference, MV_{O_2}, myocardial oxygen uptake, MGU, myocardial glucose uptake, MLE, myocardial lactate extraction $^*P<0$ 05 compared with awake, $^\dagger P<0.05$ remifentanil/propofol compared with remifentanil

	Awake	**Remifentanil**	**Remifentanil/propofol**
Epinephrine (pg ml^{-1})	115 (117)	54 (35)*	45 (24)*
Norepinephrine (pg ml^{-1})	209 (143)	111 (90)*	71 (70)*
CPP (mm Hg)	85 (11)	58 (9)*	51 (7)*
CVR (mm Hg ml^{-1} min 100 g)	0 94 (0.24)	0.82 (0.22)	0 67 (0 24)*
Myocardial blood flow (ml 100 g^{-1} min^{-1})	86 (26)	61 (11)*	65 (17)*
$AcsDo_2$ (ml)	12 1 (1 6)	9.8 (1.6)*	9 1 (1 3)†
MV_{O_2} (ml 100 g^{-1} min^{-1})	10 2 (2 3)	5.8 (0 8)*	5.7 (0.8)*
MGU (mg 100 g^{-1} min^{-1})	2.0 (2 3)	0.74 (0.41)*	0 48 (0.22)*
MLE (%)	13.3 (12.1)	9.4 (7.2)	8 4 (7 9)

ous ST-segment analysis did not detect any abnormalities in ECG leads II and V_5.

Discussion

Our data demonstrate that high-dose remifentanil and moderately dosed remifentanil combined with propofol preserve haemodynamic stability and reduce myocardial blood flow and myocardial metabolism to a similar extent in patients with coronary artery disease. We observed no significant differences between these two anaesthetic techniques with respect to systemic haemodynamic responses.

It is difficult to compare our data in detail with data from other groups, primarily because of differences in study design. Most studies investigating the haemodynamic effects of remifentanil were performed intraoperatively[10 11] and did not include measurement of cardiac output. Our study was performed in patients before CABG surgery after standardized premedication with flunitrazepame 2 mg orally the evening before surgery and the morning of surgery to minimize the risk of awareness during the study period under high-dose opioid anaesthesia.

Warner and co-workers[10] found a decrease in heart rate and MAP after application of remifentanil, which is in line with our results. In other studies, sufentanil[12] and fentanyl[13] reduced MAP by 15% and 26%, respectively, and CI by 28% and 21%, respectively. In contrast to sufentanil and fentanyl, the reduction in CI induced by remifentanil was accompanied by a decrease in heart rate. However, severe bradycardia has been reported after administration of remifentanil[14 15] and after administration of sufentanil.[16 17] The administration of muscle relaxants without vagolytic properties,[16 17] or pretreatment with drugs with negative chronotropic properties, such as calcium channel blockers or beta-blockers,[14] may contribute to the occurrence of bradycardia. In our study 58% of patients were pretreated with a beta-blocker. In these patients the decrease in heart rate did not differ from that in patients without beta-blockade. Severe bradycardia did not occur in any patient during the period of investigation. The lowest heart rate (45 beats min^{-1}) occurred in a patient (no. 12) pretreated with beta-blockers. However, this patient had a low heart rate when awake, and so the change in heart rate induced by remifentanil did not differ from the mean change.

Warner and co-workers reported that the haemodynamic effects of remifentanil were dose-dependent, but this result could not be reproduced by Sebel and colleagues,[11] who found a dose-independent decrease in heart rate, diastolic and systolic blood pressure. The difference in the results of these two studies may have been caused by the use of variable concentrations of isoflurane. The study protocol of these studies allowed the additional use of isoflurane in order to complete the insufficient blockade of sympathetic responses to surgical stimuli by opioids.[12 18 19] Another argument for supplementing remifentanil with other anaesthetics is that loss of consciousness is incomplete when remifentanil is used as the sole anaesthetic agent, even in extremely high doses.[20] In order to study an anaesthetic regime which can be applied to clinical practice, we thus investigated not only high-dose remifentanil but also moderately dosed remifentanil combined with a target-controlled infusion of propofol. It is known from a variety of studies that the target-controlled infusion based upon a pharmacokinetic model may produce more reliable plasma concentrations.[21 22]

Stephan and colleagues[23] found that, after induction of anaesthesia with propofol, CI was reduced by 19% whereas heart rate increased by 12%. After administration of fentanyl and during sternotomy, CI remained unchanged and heart rate returned to values obtained in the awake patient. Despite the different study design we found similar changes in CI during remifentanil/propofol anaesthesia. Some study groups have found that heart rate is unchanged or increases during total intravenous anaesthesia with propofol,[23 24] but our results were in line with the findings of other study groups.[25 26] In contrast to the results of Stephan and colleagues,[23] we found that SVRI was lower after supplementation of propofol than during the awake period, which may be explained by the lack of surgical stimulus in our study. During the period of high-dose remifentanil anaesthesia, SVRI showed a tendency to decrease but did not change significantly.

During the high-dose remifentanil period in our study, the 32% decrease in coronary perfusion pressure was paralleled by a 30% decrease in myocardial blood flow. Myocardial oxygen uptake decreased by 42% while coronary vascular resistance remained unchanged. Our findings were comparable to those from other studies which showed that coronary vascular resistance did not change after application of morphine,[18] fentanyl[27] or sufentanil.[12 27] In these studies the reported decreases in coronary perfusion pressure and myocardial blood flow were less than those in our study. It can be argued that the decreased coronary perfusion pressure found in our study would risk impairment of coronary perfusion in areas supplied by stenotic coronary arteries. Yet we found a decrease in arterial coronary sinus oxygen content difference, implying that global myocardial oxygen supply increased.

During the period of remifentanil/propofol anaesthesia, myocardial blood flow decreased by only 25% whereas coronary perfusion pressure decreased by 40%. As a result, the calculated coronary vascular resistance decreased significantly, by 29%. This finding was in contrast to the finding of Stephan and co-workers,[23] who found an increased coronary vascular resistance during fentanyl/propofol anaesthesia. In addition to the differing pharmacodynamic properties of the opioids, differences in study design may explain this discrepancy, as measurements of myocardial dynamics were performed during sternotomy. Thus, the increase in coronary vascular resistance found by Stephan and colleagues may have resulted from a sympathetic response to the surgical stimulus. In our study the decrease in coronary vascular resistance cannot be explained by increased metabolic needs. Myocardial oxygen uptake decreased during remifentanil/propofol anaesthesia to a greater extent than myocardial blood flow, resulting in a 25% decrease in arterial coronary sinus oxygen content difference. Thus, the decrease in the coronary vascular resistance seems to be induced by vasodilating effects of propofol. Our technique for measuring myocardial blood flow cannot be used to investigate the regional distribution of myocardial blood flow, so we cannot determine if coronary vasodilation was limited to epicardial vessels or if it was distributed homogeneously. However, none of the investigated patients showed a negative myocardial lactate extraction or electrocardiographic signs of myocardial ischaemia throughout the period of investigation.

In conclusion, the haemodynamic effects of high-dose remifentanil are similar to those of remifentanil/propofol anaesthesia. Neither of these anaesthetic techniques impairs the balance of MVO_2 or oxygen supply in patients before CABG surgery.

References

1 Fishman RL, Harvey SC, Zellner JL, Pinosky ML, Handy JR Reducing cardiac surgical trauma: the minimally invasive direct coronary artery bypass. *South Med J* 1997; **90**: 965–71

2 Higgins TL. Safety issues regarding early extubation after coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 1995; **9** (Suppl 1): 24–9

3 Kapila A, Glass PS, Jacobs JR *et al.* Measured context-sensitive half-times of remifentanil and alfentanil. *Anesthesiology* 1995; **83**: 968–75

4 Egan TD. Remifentanil pharmacokinetics and pharmacodynamics. A preliminary appraisal. *Clin Pharmacokinet* 1995; **29**: 80–94

5 Dershwitz M, Hoke JF, Rosow CE *et al.* Pharmacokinetics and pharmacodynamics of remifentanil in volunteer subjects with severe liver disease. *Anesthesiology* 1996; **84**: 812–20

6 Royston D. Remifentanil in cardiac surgery. *Eur J Anaesthesiol Suppl* 1995; **10**: 77–9

7 Bacon R, Chandrasekan V, Haigh A, Royston BD, Royston D, Sundt T. Early extubation after open-heart surgery with total intravenous anaesthetic technique. *Lancet* 1995; **345**: 133–4

8 Kety SS, Schmidt CF. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure and normal values. *J Clin Invest* 1948; **27**: 476–83

9 Rau G, Tauchert M, Bruckner JB, Eberlein HJ, Bretschneider HJ. Measurement of the coronary blood flow with argon-foreign gas method in the patient. *Verh Deutsch Ges Kreislaufforsch* 1968; **34**: 385–93

10 Warner DS, Hindman BJ, Todd MM *et al.* Intracranial pressure and hemodynamic effects of remifentanil versus alfentanil in patients undergoing supratentorial craniotomy. *Anesth Analg* 1996; **83**: 348–53

11 Sebel PS, Hoke JF, Westmoreland C, Hug-CC R, Muir KT, Szlam F. Histamine concentrations and hemodynamic responses after remifentanil. *Anesth Analg* 1995; **80**: 990–3

12 Sonntag H, Stephan H, Lange H, Rieke H, Kettler D, Martschausky N. Sufentanil does not block sympathetic responses to surgical stimuli in patients having coronary artery revascularization surgery. *Anesth Analg* 1989; **68**: 584–92

13 Sonntag H, Larsen R, Hilfiker O, Kettler D, Brockschnieder B. Myocardial blood flow and oxygen consumption during high-dose fentanyl anesthesia in patients with coronary artery disease *Anesthesiology* 1982; **56**: 417–22

14 Dershwitz M, Randel GI, Rosow CE *et al.* Initial clinical experience with remifentanil, a new opioid metabolized by esterases. *Anesth Analg* 1995; **81**: 619–23

15 DeSouza G, Lewis MC, TerRiet MF. Severe bradycardia after remifentanil. *Anesthesiology* 1997; **87**: 1019–20

16 Starr NJ, Sethna DH, Estafanous FG Bradycardia and asystole following the rapid administration of sufentanil with vecuronium. *Anesthesiology* 1986; **64**: 521–3

17 Sherman EP, Lebowitz PW, Street WC. Bradycardia following sufentanil–succinylcholine. *Anesthesiology* 1987, **66**: 106

18 Hilfiker O, Larsen R, Brockschnieder B, Sonntag H Morphine 'anesthesia'–coronary blood flow and oxygen consumption in patients with coronary artery disease. *Anaesthesist* 1982; **31**· 371–6

19 Philbin DM, Rosow CE, Schneider RC, Koski G, D'Ambra MN. Fentanyl and sufentanil anesthesia revisited: how much is enough? *Anesthesiology* 1990; **73**: 5–11

20 Jhaveri R, Joshi P, Batenhorst R, Baughman V, Glass PS. Dose comparison of remifentanil and alfentanil for loss of consciousness. *Anesthesiology* 1997, **87**: 253–9

21 Schüttler J, Kloos S, Schwilden H, Stoeckel H. Total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion. *Anaesthesia* 1988; **43** (Suppl): 2–7

22 Coetzee JF, Glen JB, Wium CA, Boshoff L. Pharmacokinetic model selection for target controlled infusions of propofol. Assessment of three parameter sets. *Anesthesiology* 1995, **82**. 1328–45

23 Stephan H, Sonntag H, Schenk HD, Kettler D, Khambatta HJ Effects of propofol on cardiovascular dynamics, myocardial blood flow and myocardial metabolism in patients with coronary artery disease. *Br J Anaesth* 1986; **58**: 969–75

24 Prys-Roberts C, Davies JR, Calverley RK, Goodman NW. Haemodynamic effects of infusions of diisopropyl phenol (ICI 35 868) during nitrous oxide anaesthesia in man. *Br J Anaesth* 1983; **55**: 105–11

25 Patrick MR, Blair IJ, Feneck RO, Sebel PS. A comparison of the haemodynamic effects of propofol ('Diprivan') and thiopentone in patients with coronary artery disease. *Postgrad Med J* 1985, **61** (Suppl 3): 23–7

26 Seitz W, Lubbe N, Schaps D, Haverich A, Kirchner E. Propofol for induction and maintenance of anesthesia during heart surgery. Results of pharmacological studies in man *Anaesthesist* 1991; **40**· 145–52

27 Larsen R, Sonntag H, Schenk HD, Radke J, Hilfiker O. Haemodynamics, coronary blood flow and myocardial metabolism in man: effects of sufentanil and fentanyl. *Anaesthesist* 1980, **29**. 277–9

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Severe carbon monoxide poisoning: outcome after hyperbaric oxygen therapy

M. Hawkins[1]*, J. Harrison[1 2] and P. Charters[1 2]

[1]*University Hospital Aintree, Liverpool, UK.* [2]*North-West Emergency Recompression Unit, Wirral, Merseyside, UK*

**Corresponding author: Department of Anaesthesia, University Hospital Aintree, Liverpool L9 7AL, UK*

This paper reports the outcome after carbon monoxide poisoning in 31 consecutive patients treated with mechanical ventilation and hyperbaric oxygen therapy, compared with another study of mechanically ventilated patients treated with normobaric oxygen. We found 16.1% hospital mortality and 3.8% severe short-term memory loss, compared with 30% hospital mortality and 20% incidence of serious neurological deficit after treatment with normobaric oxygen; outcome was poor in 19.4% and 44.3% of those treated with hyperbaric and normobaric oxygen, respectively ($P<0.05$). Cerebral oedema caused three of five deaths despite hyperbaric therapy, occurring at 24–48 h after poisoning. Intracranial pressure monitoring and CT scan of the head before wakening should be considered in any severely poisoned patient.

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Carbon monoxide poisoning is an important cause of morbidity and mortality. There is no reliable marker of severity of poisoning, with clinicians relying on features such as level of consciousness and cardiac abnormalities. Carbon monoxide combines with haemoglobin to form carboxyhaemoglobin (Hb-CO), normal concentrations of which are approximately 2% in non-smokers and 3–8% in smokers. Acute Hb-CO measurements can confirm exposure, but Hb-CO concentrations do not correlate with severity of poisoning. Hyperbaric oxygen therapy is generally regarded as the treatment of choice for moderate to severe carbon monoxide poisoning[1] but on the UK mainland there are currently only seven hyperbaric units with facilities to treat critically ill patients. The North-West Emergency Recompression Unit (NWERU) is such a unit in the Mersey region.

In 1988, Krantz and colleagues[2] reviewed the outcome of 79 patients with severe carbon monoxide poisoning requiring mechanical ventilation, who did not receive hyperbaric oxygen therapy. Hospital mortality was 30%, and 20% of survivors were discharged with significant brain damage, often into long-term care after prolonged hospitalization. We report a retrospective study of the current outcome from hyperbaric oxygen therapy, that is, therapy with 100% oxygen at 2.8 atmospheres absolute pressure for 1–1.5 h,[3] for severely poisoned patients receiving intensive care.

Methods

We reviewed the case records of 31 consecutive patients requiring mechanical ventilation for severe carbon monoxide poisoning treated at NWERU between November 1995 and January 1999. Information on patients' clinical state at the time of discharge was obtained from hospitals and, where possible, more long-term information was obtained from general practitioners (GPs).

Results were analysed with a chi-squared test for binomial (good/poor) outcomes. The Mann–Whitney *U*-test was used to compare Hb-CO and standard bicarbonate concentrations between those with a good or poor outcome.

Results

Seventeen (54.8%) of the 31 patients were poisoned with car exhaust fumes, one unintentionally. Ten patients (32.3%) were involved in house fires and four (12.9%) were poisoned by faulty heating installations. Before hyperbaric oxygen therapy, all patients had been treated with 100% oxygen and were subsequently admitted to an intensive care unit in the Mersey area. Seven patients received only one treatment with hyperbaric oxygen; three of these died before further therapy could be given, while the other four appeared to recover well despite missing further therapy.

Five (16.1%) of the patients died in hospital; three of these had poisoned themselves and two had been involved in house fires (neither had severe burns). One patient died

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Table 1. Summary of patient characteristics and outcome. The results for Hb-CO and standard bicarbonate are shown as range (median). The proportion of patients with poor outcome in the two groups was significantly different ($P<0.05$)

	Normobaric treatment	**Hyperbaric treatment**
No. of patients	79	31
Age (yr), range (median)	5–91 (49)	21–78 (41)
Gender, number (%)		
Male	33 (42%)	20 (64.5%)
Female	46 (58%)	11 (35.4%)
Hb-CO %	'normal'–63 (32)	12.6–52.1 (40)
Standard HCO_3 (mmol $litre^{-1}$)		
Good outcome	9.4–25.8 (20.7)	10.4–23 (19)
Poor outcome	6.8–25.2 (17.7)	6.2–16.4 (11.7)
Poor outcome	35/79 (44.3%)	6/31 (19.4%)

from multi-system organ failure, two had severe cerebral oedema and one had cerebral oedema and extensive bowel infarction. The exact cause of death could not be determined for the fifth patient. Another patient suffered severe short-term memory loss requiring rehabilitation therapy so that, in all, six patients were considered to have a poor outcome. Of the five who died, three had received prolonged life-support measures following cardiorespiratory arrest before treatment with hyperbaric oxygen. The only biochemical difference that was detected between patients with a good outcome and those with a poor outcome was a lower standard bicarbonate concentration ($P<0.005$) in the latter (Table 1).

Patient characteristics were broadly similar to those reported by Krantz and colleagues[2] and there was no difference in standard bicarbonate concentrations (Table 1). There were fewer cases with poor outcome in our survey ($P<0.05$), but the difference in hospital mortality between the two groups was not significant ($P=0.02$).

GPs provided further information about 10 patients. Four patients had some neurological symptoms (gait disturbance, short-term memory loss and fatigue) after their poisoning; all of these patients recovered spontaneously within a few weeks. One patient continued to complain of fatigue, headache and short-term memory problems up to a year later, though these symptoms had been present before the poisoning.

Discussion

Controversy persists over the most appropriate treatment for carbon monoxide poisoning.[4] Many patients with mild poisoning make a full recovery whatever the treatment, but approximately 1000 patients die each year in the UK as a result of carbon monoxide poisoning.[5] Even after initial recovery, there is a risk of delayed neurological sequelae. Current criteria for the treatment of carbon monoxide poisoning with hyperbaric oxygen[6] are as follows: carboxyhaemoglobin >20%; loss of consciousness at any stage; neurological signs or symptoms other than headache; myocardial ischaemia or arrhythmia diagnosed by ECG; pregnancy.

All patients in this report required tracheal intubation before transfer for therapy with hyperbaric oxygen; in three cases the incident had been severe enough to cause the death of other casualties at the scene.

Our study supports the findings of Krantz and colleagues,[2] in that the level of Hb-CO was of no prognostic value, though metabolic acidosis on arrival to hospital was greater in those who did badly. Overall, the severity of metabolic acidosis was comparable between the two studies, but outcome was significantly better in patients treated with hyperbaric oxygen. Many of the patients in the report by Krantz and colleagues subsequently needed institutional care owing to the severity of their neurological deficit. This did not happen for any of the patients treated with hyperbaric oxygen.

The difference in hospital mortality between the two groups was not significant, maybe because of differences in the size of groups. If the hyperbaric group size had been twice as large, a 16.1% mortality would have been significantly less (at the 5% level). Even with hyperbaric therapy, some patients developed delayed neurological sequelae. Four of the survivors who could be traced complained to their GP with minor neurological sequelae, namely headache, fatigue, gait disturbance or mild short-term memory loss.

The two studies were conducted at different times, so intensive care treatment was probably not similar. Krantz and colleagues reported a high incidence of hypotension from the treatment used to prevent cerebral oedema, and moderate hypothermia was used for cerebral protection. The patients treated hyperbarically received cardiovascular support, and were warmed to achieve and maintain normal temperature. A more recent study, on animals, reported that hypothermia was associated with a worse outcome in carbon monoxide poisoning.[7] Krantz and colleagues did not report the exact duration of treatment with 100% oxygen, saying only that it was at least 1 h. Current guidelines would recommend 6 h.[8]

The results of this study have led to a change in our practice. Severe cerebral oedema (responsible for three of the five deaths in this study) was an unpredictable problem at 24–48 h, so we now consider monitoring intracranial pressure and/or a doing a CT scan of the head before wakening.

The risks associated with hyperbaric oxygen therapy are well documented.[9] It is common practice to inflate the tracheal tube cuff with saline to avoid compression and expansion of an air-filled cuff with changes in ambient pressure. In one patient, the cuff was overinflated at the referring hospital, resulting in a tracheal mucosal tear; this healed without intervention, but prolonged the patient's ICU stay.

To obtain maximal benefit, hyperbaric oxygen should be administered within 6 h of a patient's removal from carbon monoxide.[10] Although patients were transported over long distances, most (25/31) received treatment within 6 h (maximum interval 8 h 12 min). There was no evidence that the long journeys caused complications.

In conclusion, hyperbaric oxygen treatment of severely poisoned patients appeared to reduce the risk of serious neurological deficit and the need for prolonged care.

References

1 Mathieu D, Wattel F, Nevière R, Mathieu-Nolf M. Carbon monoxide poisoning: mechanism, clinical presentation and management. In: Oriani G, Marroni A, Wattel F, eds. *Handbook on Hyperbaric Medicine*. Milan: Springer-Verlag, 1996; 281–96

2 Krantz T, Thisted B, Strøm J, Sørensen MB. Acute carbon monoxide poisoning. *Acta Anaesthesiol Scand* 1988; **32**: 278–82

3 Undersea and Hyperbaric Medicine Society. *Hyperbaric Oxygen Therapy: A Committee Report. 30 CR (HBO)*. 1992; 12–13.

4 VanMeter KW, Weiss LD, Harch PG, Andrews LC, Simanonok JP, Staab PK, Gottlieb SF. Should the pressure be off or on in the use of oxygen in the treatment of carbon monoxide poisoned patients? *Ann Emerg Med* 1994; **24**: 283–8

5 Meredith T, Vale A. Carbon monoxide poisoning. *Br Med J* 1988; **296**: 77–8

6 Chief Medical Officer and Chief Nursing Officer. *Carbon Monoxide: the Forgotten Killer*. London, Department of Health. 1998.

7 Sutariya BB, Penney DG, Nallamothu BG. Hypothermia following acute carbon monoxide poisoning increases mortality. *Toxicol Lett* 1990; **52**: 201–8

8 Raphael J-C, Elkharrat D, Jars-Guincestre M-C, Chastang C, Chasles V, Verken J-B, Gajdos P. Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. *Lancet* 1989; **ii**: 414–19

9 Tibbles PM, Edelsberg JS. Hyperbaric oxygen therapy. *New Engl J Med* 1996; **334**: 1642–8

10 Goulon M, Barois A, Rapin F, Grosbuis S, Labrousse J. Carbon monoxide poisoning and acute anoxia due to breathing coal gas and hydrocarbons. *Ann Med Intern* 1969; **120**: 335–49

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Dose requirements of infusions of cisatracurium or rocuronium during hypothermic cardiopulmonary bypass

G. Cammu*, J. Coddens, J. Hendrickx and T. Deloof

Department of Anaesthesiology and Critical Care Medicine, OLV-Ziekenhuis, Moorselbaan 164, B-9300 Aalst, Belgium

**Corresponding author. Present address: Department for Anaesthesia, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium*

We investigated the influence of mild hypothermic cardiopulmonary bypass (CPB) on the dose requirements of cisatracurium or rocuronium used as a continuous infusion. We studied eight patients given cisatracurium and nine given rocuronium. They were ASA class III and IV and scheduled for elective coronary artery bypass grafting. Neuromuscular transmission was monitored electromyographically. After recovery of T1/T0 to 10%, a cisatracurium infusion or a rocuronium infusion was started at a rate of 1.5 or 10 μg kg^{-1} min^{-1}, respectively, and adjusted to maintain T1/T0 at 15%. Infusion rate and duration were recorded before, during and after CPB in each patient and the mean infusion rates were calculated. One-way ANOVA showed a statistically significant difference between the cisatracurium infusion rates before, during and after CPB: A T1/T0 of 15% could be achieved with a mean infusion rate of 1.1, 0.75 and 0.98 μg kg^{-1} min^{-1} before, during and after CPB, respectively. There was no significant difference between the rocuronium infusion rates before, during and after CPB. The mean rocuronium infusion rate required to maintain T1/T0 at 15% throughout the procedure was 4.1 μg kg^{-1} min^{-1}. Cisatracurium infusion rates should be halved during CPB. Even after CPB, requirements are reduced. The same tendency occurs with rocuronium, but the changes in infusion rate were not statistically significant.

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Neuromuscular blocking drugs are commonly used during coronary artery bypass grafting (CABG). Their advantages are that they aid mechanical ventilation, decrease anaesthetic requirements, prevent patient movement and decrease oxygen consumption. Cisatracurium and rocuronium generally lack cardiovascular side-effects during high-dose opioid anaesthesia[1 2] and thus have advantages for use during CABG procedures. These advantages may not, however, be observed in different clinical conditions.[3] During CABG and, more particularly, during cardiopulmonary bypass (CPB), cisatracurium and rocuronium requirements have not been studied in detail.

Drug elimination may be reduced by relative hypoperfusion of the liver and kidney or by hypothermia during CPB.[4] This is true for atracurium[5] and for rocuronium.[6] Moreover, as the clearance of cisatracurium, one of the stereoisomers of atracurium, is highly dependent on Hofmann degradation,[7] temperature and pH changes associated with CPB are likely to affect its pharmacokinetics more than those of other neuromuscular blocking drugs. As data for the newer neuromuscular blocking drugs are scarce, cisatracurium and rocuronium infusion rates during and after CPB are adjusted empirically.

A more rational dosage regimen may reduce waste and, consequently, the cost of using these expensive new drugs. Moreover, a more predictable recovery may be important in fast tracking and minimally invasive cardiac procedures, as it may allow early extubation. Avoiding an excessively prolonged neuromuscular block may also decrease the incidence of awareness during the first hours on the intensive care unit (ICU).

Methods

After Institutional Review Board approval and written informed consent, we studied eight patients given cisatracurium followed by nine given rocuronium during CABG with mild hypothermic CPB (33°C). All patients were ASA class III and IV. Exclusion criteria were: left ventricular ejection fraction <50%; evidence of renal, hepatic, metabolic or

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neuromuscular disorders; and history of medication interfering with neuromuscular transmission.

All patients were premedicated with lorazepam 2.5 mg 1 h before induction. After 3 min of preoxygenation, anaesthesia was induced with diazepam 0.15 mg kg^{-1} and sufentanil 5 µg kg^{-1} i.v. As soon as the eyelid reflex was absent, assisted ventilation by facemask was started with oxygen 100%. After equipotent bolus doses of cisatracurium 0.1 mg kg^{-1} or rocuronium 0.6 mg kg^{-1} intubation was performed as soon as the first response to the train-of-four (TOF) stimulus (T1) fell below 10%. Normocapnic ventilation was established with a Servo 900C (Siemens Elema; Stockholm, Sweden). Anaesthesia was maintained with oxygen 50% in air, propofol 1–3 mg kg^{-1} h^{-1} and supplemental boluses of diazepam or sufentanil. No potent inhalation anaesthetics were used. Routine monitoring included ECG, pulse oximetry, invasive arterial pressure (left radial artery) and central venous pressure (right jugular vein). Temperature was monitored at the following sites: oesophagus, rectum, skin of the forehead and the area of skin on the right arm where neuromuscular transmission monitoring electrodes had been applied.

The bypass circuit was of standard construction. Blood temperature was measured at the venous site of the bypass circuit and kept constant at 33°C during hypothermia. Rewarming to 37°C was started as soon as the surgeon had completed the last distal anastomosis. Alpha-stat pH management was used.

Neuromuscular transmission was monitored on the right arm by the EMG response of the adductor pollicis muscle to TOF stimulation of the ulnar nerve, using surface electrodes (M-NMT module; Datex-Ohmeda, Helsinki, Finland). The right arm was wrapped in a protective towel. The TOF response to a supramaximal stimulus was obtained before the initial bolus of neuromuscular blocking drug. The stimulus current range during supramaximal stimulation was 10–70 mA. The TOF was measured at 1 min intervals, using a square wave, constant current stimulus pulse with a width of 200 µs.

After recovery of T1/T0 to 10%, patients were given either cisatracurium or rocuronium, at an infusion rate of 1.5 and 10 µg kg^{-1} min^{-1}, respectively. These dosages were based on data obtained during major non-cardiac surgery.[8 9] The infusion rate was adjusted to maintain T1/T0 at 15%. The concentration of the solutions used for infusion was 0.2 and 1 mg ml^{-1} for cisatracurium and rocuronium, respectively, so that even small changes in infusion rate led to significant changes of volume delivered and, thus, to a quick alteration in effect. The infusion was discontinued just before the completion of surgery. Bolus doses of cisatracurium 0.03 mg kg^{-1} or rocuronium 0.15 mg kg^{-1} were given if gross movement occurred. Spontaneous recovery from neuromuscular blockade was allowed on the ICU. The results of monitoring neuromuscular transmission and all other vital parameters were displayed on a Datex AS/3 monitor and stored in a spreadsheet on a PC (Compaq).

Table 1. Patient characteristics in cisatracurium and rocuronium groups

	Cisatracurium group ($n=8$)	**Rocuronium group ($n=9$)**
Age, yr (mean (range))	71 (62–80)	70 (62–77)
Gender, male/female	4/4	7/2
Weight, kg (mean (SD))	76 (19)	73 (15)
Height, cm (mean (SD))	162 (11)	166 (10)

Table 2. Mean (SD) cisatracurium and rocuronium infusion rates during coronary artery bypass grafting (one-way ANOVA; significance at $P<0.05$)

	Infusion rate, µg kg^{-1} min^{-1}			
	Before bypass	**During bypass**	**After bypass**	***P***
Cisatracurium	1.10 (0.24)	0.75 (0.24)	0.98 (0.17)	0.01
Rocuronium	4.42 (1.83)	3.57 (1.54)	4.24 (1.45)	0.5

Infusion rate and infusion duration were recorded before, during and after CPB for each patient. The mean infusion rates in both groups were derived before, during and after bypass. Statistical analysis included one-way analysis of variance (ANOVA). Significance was set at a level of $P<0.05$. A one-sample *t*-test was performed to assess if the derived mean (actual T1/T0%) was significantly different from the theoretical mean (T1/T0=15%). Results are presented as mean (SD).

Results

Anaesthesia was uneventful in all patients. No patient moved and no diaphragmatic contractions were observed. There was no need for any escape bolus dose of neuromuscular blocking drug. Patients did not sweat and their eyes did not water. They did not recall the operation. One patient in the cisatracurium group suffered from opioid-induced rigidity during induction. Although assisted ventilation was initially difficult, oxygenation was well maintained and induction was otherwise uneventful.

Table 1 shows the physical characteristics of the patients in the cisatracurium and rocuronium groups. The mean (SD) time between starting the initial infusion of cisatracurium at a rate of 1.5 µg kg^{-1} min^{-1} and the first adjustment to a lower dose was 34.5 (19.1) min. In the cisatracurium group, mean (SD) T1/T0 during the procedure was 14.6 (9.9)%. This actual mean was not significantly different from the preset value (T1/T0=15%) ($P=0.7$). Table 2 shows the one-way ANOVA of cisatracurium infusion rates during CABG. The means differ significantly ($P=0.01$), with the highest rate before and the lowest during CPB.

The mean (SD) time between starting the rocuronium infusion at the initial infusion rate (10 µg kg^{-1} min^{-1}) and the first adjustment to a lower dose was 20.2 (13.3) min. In the rocuronium group, the mean (SD) T1/T0 during the procedure was 14.2 (7.1) %; this was not significantly different from the preset value (T1/T0=15%) ($P=0.2$). Table 2 shows the one-way ANOVA of rocuronium infusion rates during CABG. There was no statistically significant difference between these means (P=0.5). The mean (SD) infusion rate of rocuronium required to keep T1/T0 at 15% throughout surgery was 4.1 (1.6) μg kg^{-1} min^{-1}.

Discussion

During hypothermic CPB, complex changes in drug pharmacokinetics occur, prolonging the duration of action of many non-depolarizing neuromuscular blocking drugs.[4] The serum concentration of neuromuscular blocking drugs may decrease when bypass is started, as a result of haemodilution,[10 11] or it may increase secondary to decreased clearance and altered drug distribution.[12 13]

The impairment of the metabolic function of the kidney, as a result of hypoperfusion during CPB is expected to decrease renal elimination.[14] Moreover, decreased hepatic blood flow, decreased concentration of binding proteins and decreased intrinsic activity of the liver are assumed to diminish hepatic clearance during bypass.[14] These phenomena may result in a steady increase in the serum concentration of neuromuscular blocking drugs during hypothermic CPB.[14] Hypothermia itself can alter the pharmacokinetics of drugs during CPB: it influences the enzymatic processes involved in drug metabolism in the liver and kidneys.[4]

Finally, since neuromuscular blocking drugs may redistribute significantly to the lungs, they can accumulate there before bypass begins. These drugs can thus become trapped in the lungs during CPB, as circulation to the lungs during that period is restricted to the bronchial vessels. When pulmonary artery blood flow is restored during weaning from CPB, the serum concentration of these drugs may suddenly increase.[4 14]

Rosen and Rosen[4] concluded that pharmacokinetics during CPB depend mainly on the composition of the oxygenator, the physical properties of the drug, the use of pulsatile or non-pulsatile flow and hypothermia. Drugs with a smaller distribution volume are more affected. The oxygenator binds lipophilic drugs more avidly than those that are hydrophilic. Neuromuscular blocking drugs generally have a rather small distribution volume: cisatracurium has a slightly greater volume of distribution than atracurium,[15] while rocuronium has a smaller one than vecuronium.[16]

In clinical practice, serum concentrations of neuromuscular blocking drugs are not available. The degree of muscle relaxation can only be assessed by monitoring neuromuscular transmission. However, neuromuscular monitoring during hypothermia is complicated by the fact that cooling affects nerve conduction, neuromuscular transmission and muscular activity.[17] The evoked response obtained in a peripheral muscle during CPB may be influenced by peripheral and core temperature gradients and alterations in skeletal muscle blood flow. Nevertheless, in the presence of hypothermia, pH disturbances and the side-effects of vasoactive drugs, neuromuscular monitoring is superior to simple clinical judgment.[18]

It has been shown that, for various neuromuscular blocking drugs, the duration of action is prolonged by CPB.[10–14 19] The half-life of cisatracurium is presumably prolonged during hypothermic CPB, as its breakdown is even more dependent on temperature and pH than that of atracurium, for which a reduced dose requirement has been observed during CPB.[5] The remainder of the drug, about 15%, is cleared by the kidneys.[15] The pharmacokinetics of rocuronium resemble those of vecuronium, except that the former has a smaller volume of distribution.[16] The termination of the effect of rocuronium is similar to vecuronium and mainly dependent on redistribution, by hepatic uptake, followed by biliary elimination. A smaller proportion, <20%, is excreted renally.[20] Smeulers and colleagues[6] found that hypothermic CPB prolonged the duration of action of maintenance doses of rocuronium.

In a preliminary study,[21] we concluded that a cisatracurium infusion, administered at half the initial rate (0.75 μg kg^{-1} min^{-1}) during hypothermic CPB, resulted in clinically acceptable conditions. Discontinuation of the cisatracurium infusion at the start of CPB, on the contrary, led to an unacceptably high incidence of movement, suggesting that it is preferable to use a continuous infusion of neuromuscular blocking agent during CABG and CPB. In the current study, we confirmed our previous findings that a cisatracurium infusion rate of 0.75 μg kg^{-1} min^{-1} was appropriate during CPB. Moreover, we found that a T1/T0 of 15% could be achieved before CPB with a dose of <1.5 μg kg^{-1} min^{-1}. Even after the bypass, cisatracurium infusion rates were lower than those before bypass, probably because of a further fall in body temperature, a tendency described in previous reports for other neuromuscular blocking drugs.[5] Less rocuronium was required during and, to a lesser extent, after CPB compared with before CPB, but the differences in infusion rates were not statistically significant. In the rocuronium group, we also observed a temperature afterdrop in the period after the bypass.

We have searched for a practical and adequate infusion regimen for the two latest commercially available neuromuscular blocking drugs, cisatracurium and rocuronium, during cardiac surgery with mild hypothermic CPB. For cisatracurium, we found that a significant reduction to half of the initial infusion rate during CPB was appropriate in clinical practice. As with atracurium, the cause is probably related to the temperature-dependent inactivation of cisatracurium. For rocuronium, a lower infusion rate was used in our study than in previous reports.[9] Further reduction during CPB was not necessary. The degree of cooling during CPB may explain the discrepancy between our results and those of other investigators: while Smeulers and colleagues[6] cooled patients to 25–28°C, we used only mild hypothermia (33°C).

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References

1 Konstadt SN, Reich DL, Stanley TE *et al.* A two-center comparison of the cardiovascular effects of cisatracurium (Nimbex™) and vecuronium in patients with coronary artery disease. *Anesth Analg* 1995; **81**: 1010–4

2 Nitschmann P, Oberkogler W, Hertsig M, Schwarz S. Comparison of haemodynamic effects of rocuronium bromide with those of vecuronium in patients undergoing CABG surgery. *Eur J Anaesth* 1994; **11**: 113–5

3 Stevens JB, Hecker RB, Talbot JC, Walker SC. The haemodynamic effects of rocuronium and vecuronium are different under balanced anaesthesia. *Acta Anaesthesiol Scand* 1997; **41**: 502–5

4 Rosen DA, Rosen KR. Elimination of drugs and toxins during cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1997; **11**: 337–40

5 Flynn PJ, Hughes R, Walton B. Use of atracurium in cardiac surgery involving cardiopulmonary bypass with induced hypothermia. *Br J Anaesth* 1984; **56**: 967–72

6 Smeulers NJ, Wierda JMKH, Van den Broek L, Gallandat Huet RCG, Hennis PJ. Effects of hypothermic cardiopulmonary bypass on the pharmacodynamics and pharmacokinetics of rocuronium. *J Cardiothorac Vasc Anesth* 1995; **9**: 700–5

7 Welch RM, Brown A, Dahl R. The degradation and metabolism of 51W89, the *R cis–R*′ *cis* isomer of atracurium in human and rat plasma. *Anesthesiology* 1994; **81**: A1091

8 Mellinghoff H, Radbruch L, Diefenbach C *et al* A comparison of cisatracurium and atracurium: onset of neuromuscular block after bolus injection and recovery after subsequent infusion. *Anesth Analg* 1996; **83**: 1072–5

9 Sparr HJ, Khuenl-Brady KS, Eriksson LI. Pharmacodynamics and pharmacokinetics of rocuronium following continuous infusion in patients during intravenous anaesthesia. *Eur J Anaesth* 1994; **11**: 63–5

10 Avram MJ, Shanks CA, Henthorn TK, Ronai AK, Kinzer J, Wilkinson CJ. Metocurine kinetics in patients undergoing operations requiring cardiopulmonary bypass. *Clin Pharmacol Ther* 1987; **42**: 576–81

11 D'Hollander AA, Duvaldestin P, Henzel D, Nevelsteen M, Bomblet JP. Variations in pancuronium requirement, plasma concentration, and urinary excretion induced by cardiopulmonary bypass with hypothermia. *Anesthesiology* 1983; **58**: 505–9

12 Shanks CA, Ramzan IM, Walker JS, Brown KF. Gallamine disposition in open-heart surgery involving cardiopulmonary bypass. *Clin Pharmacol Ther* 1983; **33**: 792–9

13 Walker JS, Shanks CA, Brown KF. Altered *d*-tubocurarine disposition during cardiopulmonary bypass surgery. *Clin Pharmacol Ther* 1984; **35**: 686–94

14 Buylaert WA, Herregods L, Mortier E, Bogaert M. Cardiopulmonary bypass and the pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1989; **17**: 10–26

15 Lien CA, Schmith VD, Belmont MR *et al.* Pharmacokinetics of cisatracurium in patients receiving nitrous oxide/opioid/barbiturate anesthesia. *Anesthesiology* 1996; **84**: 300–8

16 Wierda JMKH, Proost JH, Schiere S, Hommes FDM. Pharmacokinetics and pharmacokinetic/dynamic relationship of rocuronium bromide in humans. *Eur J Anaesth* 1994; **11**: 66–74

17 Buzello W, Pollmaecher T, Schluermann D, Urbanyi B The influence of hypothermic cardiopulmonary bypass on neuromuscular transmission in the absence of muscle relaxants. *Anesthesiology* 1986; **64**: 279–81

18 Booij LH, Wiedemann K Monitoring neuromuscular function in the operating theater. *Anasth Intensivther Notfallmed* 1984; **19**: 107–11

19 Buzello W, Schluermann D, Schindler M, Spillner G. Hypothermic cardiopulmonary bypass and neuromuscular blockade by pancuronium and vecuronium. *Anesthesiology* 1985; **62**: 201–4

20 Wierda JMKH, Kleef UW, Lambalk LM, Kloppenburg WD, Agoston S. The pharmacodynamics and pharmacokinetics of Org 9426, a new non-depolarizing neuromuscular blocking agent, in patients anaesthetized with nitrous oxide, halothane and fentanyl. *Can J Anaesth* 1991; **38**: 430–5

21 Cammu G, Hendrickx JFA, Coddens J, De Wolf AM, Deloof T. Comparison of two dose regimens of cisatracurium during hypothermic CABG. *Br J Anaesth* 1999; **82**: A465

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A detailed analysis of theatre training activity in a UK teaching hospital

A. K. McIndoe and S. M. Underwood

Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary, Marlborough Street, Bristol BS2 8HW, UK

We examined the placement of anaesthetists in our department over a 2 yr period. Data were collected from an in-theatre system to provide details of caseload and supervision for 34 856 operations. There was wide variation between anaesthetic sub-specialties with overall supervision levels of 35% of cases for senior house officers (SHOs) and 32% for specialist registrars (SpRs). The consultant data showed the size and areas of teaching reserve in the department. We then examined individual logbooks in order to validate our data, and departmental rotas to put these data into perspective with previous attempts to quantify trainee supervision. Supervision data derived from the rota allocations showed that 86% of SHO lists and 62% of SpR lists were scheduled to be supervised. This study has described our training activity and facilitated departmental changes, as well as highlighting the need for great care in interpreting trainee supervision data acquired from different sources, particularly when comparisons are being made.

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The implementation of a structured programme for the specialist registrar unified training grade originally cited the logbook as an integral part of the assessment of progress within each specialist module.[1] Although the Royal College of Anaesthetists requires its trainees to keep a logbook (either written in a book or stored electronically),[2–4] many trainees are unable to produce an intelligible record of their activities at Regional In-Training Assessments (RITAs). Keeping an accurate, updated, individual electronic logbook requires access to a computer and the skills to use it, as well as personal organization and enthusiasm. If complete it can give a good record of individual experience and training but on its own it does not give an accurate overview of the training offered to all the trainees by a department. On the other hand, day-to-day list allocations and session rotas can provide some overall picture of the department's activity. Planned in advance, and therefore subject to alteration, they have been used to document training levels.

Theoretically, the use of a central computerized data-entry system based in the operating theatre would enable the trainee to extract the information required to demonstrate his own experience and training as well as revealing to tutors the local activity of an entire department. Strengths and weaknesses of a hospital programme could thus be identified, enabling compensatory adjustments to be made to training schedules.

Apart from the recommended duration of senior house officer (SHO) and specialist registrar (SpR) training schemes,[2–4] we do not know what degree of supervision and experience is optimal in different sub-specialty areas. Indeed at some stages a greater degree of independence may be desirable. In the absence of clearly defined standards it is difficult for trainees and trainers alike to judge the adequacy of training. It is for this reason that we undertook a study to define the traditional norm in our teaching hospital.

Methods

Definitions

All cases performed over a 2 yr period in operating theatres by consultants, SpRs and SHOs were included. Operations were classified by surgical specialty. Urgency was defined using the modified Confidential Enquiry into Perioperative Death (CEPOD) terms of scheduled, urgent (for cases requiring surgery within 24 h) and emergency (cases requiring surgery within 1 h).[5] Supervision of a trainee was defined as the presence of a more senior anaesthetist in the same operating theatre and was further subdivided into SpR or consultant supervisor.[6]

Data collection

All theatre-based information had been entered into a commercially available computerized data collection system

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(Swiftop EDS Healthcare, Bristol, UK) at the time of operation. The system had been installed for routine use, by the Trust, in November 1993 allowing direct entry of data into a networked computer terminal located in the corner of each operating theatre. A designated nurse in each theatre was responsible for identifying all members of staff involved in the care of each patient. The anaesthetist and surgeon verified patient details, and times of arrival, transfer and discharge were recorded. The system has remained in routine use since its installation.

Data analysis

Information was downloaded from the theatre database as a series of spreadsheet files which were then imported into a copy of the FileMaker Pro Anaesthetic Logbook.[7 8] The search facility was used to identify different grades of anaesthetist and a series of standardized reports was generated to allow comparisons to be made.

Verification of data

Although it was possible to inspect the theatre database for gross errors, no other 'gold standard' existed to validate the data within it. A sample of five individual trainees' personal logbooks was therefore examined for the 2 yr study period, and the case numbers and consultant supervision rates were compared with those derived from the in-theatre data collection system.

Comparisons of data

We compared supervision of trainees over the final 5 months of the study period by counting sessions retrospectively on the departmental planning rotas. This method relied upon a manual count of solo and accompanied theatre lists, as opposed to a count of individual cases. These rotas were planned by a designated consultant anaesthetist and printed the week before their start.

Results

Of the 31 trainees in the department, six were second-year SHOs and 25 were SpRs. They were considered supervised if they were in theatre with a consultant, or if they were SHOs working with an SpR. Thus the cases were divided between consultants, who may be supervising or solo, and trainees who may be working alone or supervised. The various combinations of anaesthetic personnel in theatre are shown in the Venn diagram (Fig. 1).

Theatre system data

A total of 34 856 cases was recorded on the theatre (Swiftop) system in the 2 yr study period. These were elective and emergency cases occurring by day and night, in the week and at weekends in theatre suites around the hospital, including the labour ward theatre (but not the labour rooms). All surgical specialties are covered in our hospital except plastic surgery, burns and neurosurgery, which are referred to another hospital in the city. Cases were broken down by specialty to show the departmental caseload (Fig. 2); the largest specialty covered by the department in terms of caseload was paediatrics.

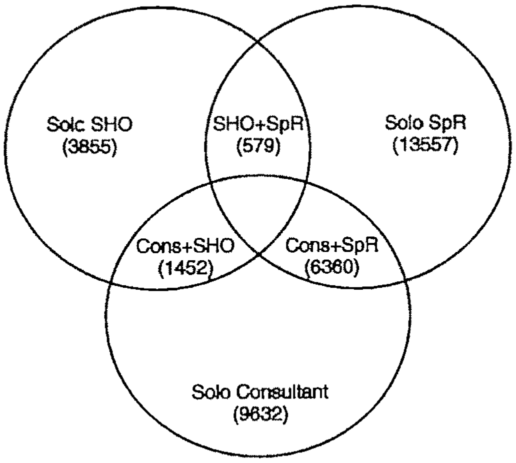

Fig 1 Venn diagram to show the possible combinations of anaesthetic personnel working alone or together (numbers of cases in parentheses)

The pattern of activity varied between the training grades (Fig. 3). Levels of supervision varied between specialties but overall supervision for the SHO and SpR grades was 35 and 32%, respectively. SHO and SpR caseload was broken down by specialty to show supervision levels (Tables 1 and 2).

Consultants were accompanied by a trainee for 45% of their cases, leaving 55% unused for teaching (Fig. 4).

Validation and comparison

The personal electronic logbooks of five trainees were compared with data from the in-theatre data collection system. Over the 2 yr period, 2284 cases were recorded by personal logbooks and 2231 for the same five anaesthetists by the in-theatre system. Therefore, 53 cases did not appear on the theatre system. Collectively, the trainee logbooks recorded an average consultant supervision rate of 29%, while the in-theatre system recorded 26% consultant supervision. Departmental rota statistics were also compared with the theatre data collected (Table 3).

Discussion

About a quarter of the SHOs' cases were orthopaedic, a quarter gynaecological, a fifth general surgery, and about a third in other specialties. In contrast, SpRs were involved in a range of different specialty areas; in our teaching hospital 30% of their caseload was paediatrics (Fig. 3).

The levels of supervision varied in different specialty areas and for the different grades of trainee anaesthetist. The supervision level for SHOs ranged from 100% in their few cardiothoracic cases to 67% for their paediatric work and 14% for orthopaedics. Some of their supervision and training came from senior trainees (SpRs) but most was from consultants (Table 1). The SpRs themselves were

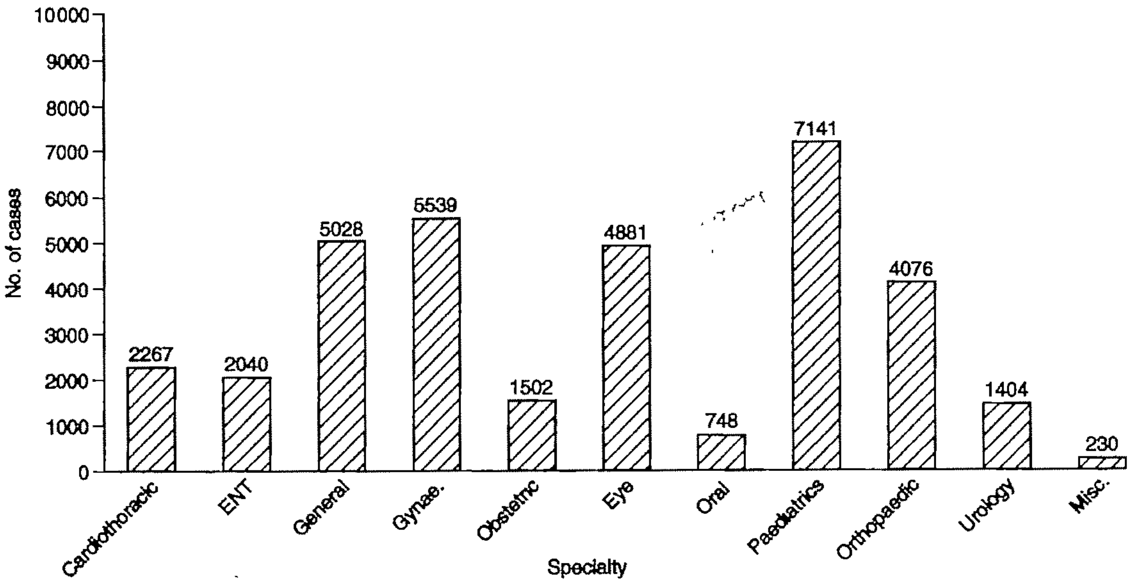

Fig 2 Departmental caseload by specialty for a 2 yr period (from Swiftop).

supervised for only 4% of orthopaedic cases, but for 48% of paediatric cases and 86% of cardiothoracic cases (Table 2). All their supervision came from consultants.

The caseload of the consultants can also be calculated from the in-theatre system (Fig. 4). Over 60% of the cases done by consultants in cardiothoracic, obstetric and paediatric surgery were used for teaching. In the cardiothoracic theatres, trainees were usually supervised (SHO, 100%; SpR, 86%) but consultants were doing 37% of their cases alone, showing that about one-third of the training potential was unused. In orthopaedics the trainees were supervised much less often (SHO, 14%; SpR, 4%) while consultants were doing 76% of the cases alone. There was thus a vast reservoir of teaching potential available even before considering what the SpRs could teach the SHOs. In obstetrics the picture is different: 32% of SHO cases and 11% of SpR cases were supervised while consultants did only 27% of cases alone. There was, therefore, much less room for additional teaching in obstetric anaesthesia in our department. We have subsequently appointed another consultant with a special interest in obstetric anaesthesia.

The difference between being taught, learning and being supervised can be great but it cannot be discerned from attendance data.[9] Indeed for trainees of different experience and in different specialties of anaesthesia, different forms of learning are probably appropriate. The level of supervision provided by a senior anaesthetist varies depending on whether they are in theatre, in the theatre suite, in the hospital or available for advice by telephone. All trainees remain nominally under the supervision of a designated consultant at all times but are to a greater or lesser extent allowed a degree of independence to develop their self-confidence and an ability to manage their own lists. At different stages of training, direct or indirect supervision may be more appropriate. Our study looked only at anaesthetists present in theatre.

The in-theatre data collection system has provided information about numbers of cases performed. Our study does not take account of the vast variation in duration of cases, and therefore the time spent in theatre. Neither does it reflect the quality of supervision or experience. The rota list counting method of measurement of supervision gives a better guide to time spent in theatre since whole lists are counted rather than individual cases. However, it suffers more than other methods from last-minute changes and staff substitutions that escape detection. Whether adequacy of training can be measured by hours spent with a senior anaesthetist or exposure to a certain number of clinical cases is, of course, another question.

The consultant caseload information provided by the theatre system allows the department to assess its teaching resource and shows clearly where there is room for more training and which areas are already saturated with trainees. It may be appropriate that a teaching hospital should offer more supervised cases in specialized areas of anaesthesia and less in those areas that are well covered in the other hospitals of a rotation. Data produced by a single hospital must always be examined with the bigger picture in mind. It is, however, useful in tuning an individual hospital's training plan to make the most of opportunities it can offer.

A degree of computer literacy is needed to operate both the computerized theatre system and individual electronic logbooks effectively, although this is small for the end user. The theatre nurses are trained to use the theatre system and must enter patient and case details as the list progresses. It is part of their routine practice and is rarely forgotten. The fact that they have no vested interest in the anaesthetic details that they enter may be of benefit to us since it is more likely to be accurate. They record only those anaesthetists in the room at the time of the procedure. The more distant supervision of trainees will, therefore, not be recorded.

The logbook system of recording caseload is only reliable if an individual completes it diligently. However, since it is the individual who benefits from accurate data entry, it may be a useful tool for the trainee. The individual logbooks kept by diligent anaesthetists are their best check on their own theatre caseload, experience and training since they show a personal perspective. They make the provision of data for RITAs easier and are an ideal way for a trainee and tutor to monitor progress. However, the use of a logbook as an audit tool focuses on activity in terms of numbers of theatre cases attended, which is easy to define. Difficulties arise when we try to apply this case-based approach to monitoring experience in the intensive care unit or for attachment to the acute pain team where interventions may be transient and experienced only as a passive observer. Attempts have been made to design logbooks which record activity in these specialist areas of anaesthetic training (see http://members.aol.com/Synaptec1/download.html), but formal agreement has not yet been reached on a common set of terms or nomenclature that adequately defines and quantifies this experience so that valid comparisons may be drawn.

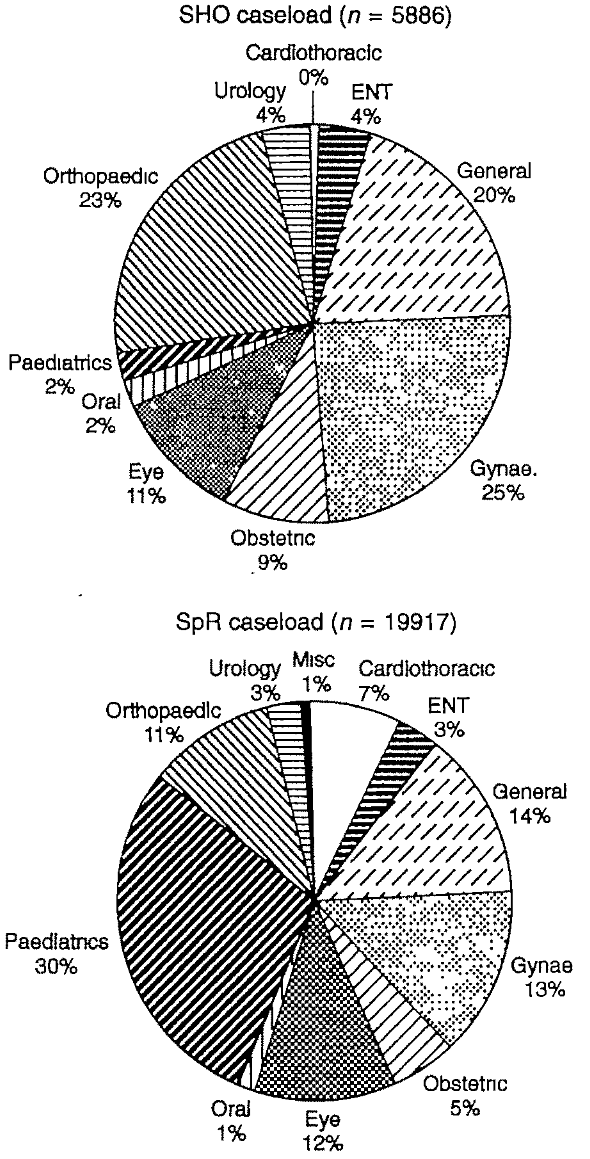

Fig 3 Pie diagrams showing pattern of caseload by specialty for anaesthetists in training

The difference between information downloaded from an in-theatre or logbook system and that counted from the departmental rotas is not surprising since these two systems do not record the same thing. Using departmental rotas to assess training activity or potential in a department is traditional but misleading. The original version, carefully planned to include variety and depth of anaesthetic experience, is frequently overtaken by events with trainees or trainers moving around to cover lists left vacant by unforeseen circumstances. Manual counting of lists from printed rotas is a time-consuming, and inaccurate, way of determining actual supervision levels of trainees. Notwithstanding the tendency to over-record supervised lists, it does count sessions rather than cases and is therefore more likely to reflect teaching time than a method that counts cases. This does emphasize the need to make clear what is being measured when trainees or departments refer to supervision level. Measurement of our trainees' supervision by in-theatre log (Swiftop) and rota methods produced very different answers, ranging from 35% of SHO cases supervised according to the theatre data to 86% SHO lists supervised from rota data. For SpRs the equivalents were 32 and 62% (Table 3). Guidelines published by the Royal College of Anaesthetists in June 1999 recommend that a

Table 1. SHO supervision shown as a percentage of cases by specialty. Data include day and night work, both elective and emergency

Specialty	Consultant	Senior trainee	Solo	Total	Supervision (%)
Cardiothoracic	27	1	0	28	100
ENT	130	32	89	251	64
General	360	180	610	1150	47
Gynaecological	226	47	1152	1425	19
Obstetric	58	111	365	534	32
Eye	292	69	266	627	58
Oral	54	14	62	130	52
Paediatrics	48	43	45	136	67
Orthopaedic	119	65	1174	1358	14
Urology	137	11	80	228	65
Miscellaneous	1	6	12	19	37
Total	1452	579	3855	5886	35

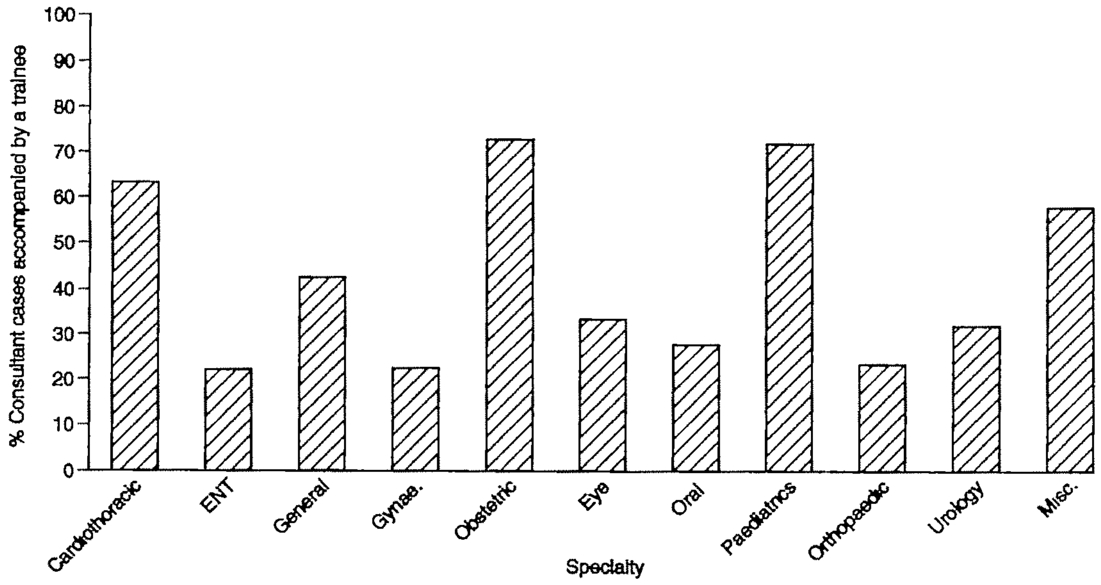

Figure 4 Consultant cases accompanied by a trainee.

Table 2 SpR supervision shown as a percentage of cases by specialty. Data include day and night work, both elective and emergency

Specialty	Consultant	Solo	Total	Supervision (%)
Cardiothoracic	1280	203	1483	86
ENT	191	498	689	28
General	632	2076	2708	23
Gynaecological	204	2452	2656	8
Obstetric	112	904	1016	11
Eye	714	1606	2320	31
Oral	78	209	287	27
Paediatrics	2847	3078	5925	48
Orthopaedic	93	2001	2094	4
Urology	156	405	561	28
Miscellaneous	53	125	178	30
Total	6360	13 557	19 917	32

Table 3. Supervision levels (%) derived by each method of assessment

	In-theatre (cases)	Department rota (lists)
SHO		
Solo	65	14
Supervised	35	86
SpR		
Solo	68	38
Supervised	32	62

minimum of 30% of elective and urgent work undertaken by trainees during daytime hours is supervised. However, the document also states that this recommendation does not apply to trainees in their early months of training or while in specialist modules.[10] Re-examination of our data to look only at daytime hours revealed that our SHOs were 43% supervised but our SpRs were only 23% supervised. Perhaps more importantly though, rigid application of this criterion excluded 2583 (44%) of the SHO cases and 12 706 (62%) of the SpR cases in our teaching hospital programme.

What is the correct level of supervision for trainees of different grades? Does this include elective and emergency work, day and night? Should it be counted from the department rota, before or after adjustments, or taken from individual logbooks, diligently completed? Or rather, should the data be downloaded from an in-theatre system in real time? These are just some of the questions that the measurement of, and therefore recommendations for, supervision of trainees poses. We have not attempted to define a standard but have described and quantified in-theatre training activity in a UK teaching hospital over a 2 yr period.

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References

1 *Specialist Training in Anaesthesia, Supervision and Assessment.* Report of the Training Methods Working Party of The Royal College of Anaesthetists. London: Royal College of Anaesthetists, 1994
2 *Specialist Training for Senior House Officers in Anaesthesia. A College Guide for the First Two Years.* London: Royal College of Anaesthetists, 1996
3 *Specialist Training in Anaesthesia. Guidelines for Educational Approval.* London: Royal College of Anaesthetists, 1996
4 *Specialist Registrars in Anaesthesia—A Training Guide* London: Royal College of Anaesthetists, 1996
5 Gallimore SC, Hoile RW, Ingram GS, Sherry KM. *The Report of the National Confidential Enquiry into Perioperative Deaths 1994/1995*, Appendix B, glossary. ISBN 0 9522069 35
6 Hammond EJ, McIndoe AK. The electronic anaesthetic logbook: the value of supervision. *Anaesthesia* 1996; **51**: 284
7 Hammond EJ, McIndoe AK. Departmental database for training *Anaesthesia* 1996; **51**: 607
8 McIndoe AK, Hammond EJ. A departmental logbook system. *Royal Coll Anaesth Newslett* 1997; **34** (Suppl.): 3–5
9 Hammond EJ, McIndoe AK. Supervision: what is more important, quantity or quality? *Anaesthesia* 1998; **53**: 205–6
10 *Guidance for Trainers.* London: Royal College of Anaesthetists, 1999

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BJA

LABORATORY INVESTIGATIONS

Chemiluminescence underestimates nitric oxide concentration in the presence of potent inhalation anaesthetics

R. Liu[1], Y. Ishibe[1]*, N. Okazaki[1] and K. Kimura[2]

[1]Department of Anaesthesiology and Reanimatology and [2]Department of Biochemistry, Tottori University Faculty of Medicine, Tottori 683-8504, Yonago, Japan

**Corresponding author*

We investigated the effect of potent inhalation anaesthetics on nitric oxide (NO) concentration measured by the chemiluminescence method. We found that the NO concentration was increasingly underestimated with increasing concentrations of halothane, isoflurane, enflurane and sevoflurane (r^2=0.918–0.997, $P<0.01$). Statistical analysis showed that the four inhalation agents at the same concentration produced a similar error in the measured NO concentration. In the presence of a fixed concentration of sevoflurane (5.0%), isoflurane (5.2%), enflurane (4.5%) or halothane (6.1%), the rate of reduction in the measured NO concentration increased in proportion to the NO concentration (r^2=0.909–0.982, $P<0.01$). No direct chemical interaction between the potent inhalation agents and NO was detected by gas chromatography–mass spectrometry. We conclude that NO concentration can be underestimated when measured by the chemiluminescence method in the presence of potent inhalation agents. This underestimation may result from emission absorption and/or the quenching phenomenon, but is not attributable to a chemical reaction between the inhalation agent and NO.

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Keywords: anaesthetics; gases; monitoring techniques; nitric oxide

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Nitric oxide (NO) is produced by cells within the respiratory tract and can be detected in the expired gas.[1–3] Measurement of airway NO production has attracted much attention in recent years.[4–6] The chemiluminescence method is commonly used for the accurate estimation of expired NO. This method is based on a gas-phase chemiluminescence reaction between NO and ozone that produces nitrogen dioxide, which is detected by a thermoelectrically cooled, red-sensitive photomultiplier tube. It is a sensitive and reliable method, but factors that influence light emission and/or detection may result in errors in the NO value. It has been reported that oxygen and humidity can affect NO measurement by the chemiluminescence method.[7–9] However, whether potent inhalation anaesthetics also affect NO measurement has not been investigated Although subtle errors in NO measurement caused by oxygen and humidity are not of significance during NO inhalation therapy, they are likely to cause misinterpretation of exhaled NO concentrations in critically ill patients. As potent inhalation agents may undergo emission absorption and the quenching phenomenon, which interferes with the quantity of the emission, we hypothesized that measurement of NO by the chemiluminescence method in the presence of potent inhalation agents may result in underestimation of NO concentration. This laboratory study was designed to examine the effect of potent inhalation anaesthetics on the measurement of NO concentration.

Materials and methods

The NO concentration was measured by a NO analyser (model 280, software version 2.05, Sievers Instruments, Boulder, CO, USA). The method of analysis was based on chemiluminescence, and had a sensitivity of 1 parts per billion (ppb) and a measurement range of 1–500 000 ppb. The sampling rate used for analysis was 50 ml min^{-1}. The original data were recorded, displayed and calculated using a MacLab system, consisting of a MacLab hardware unit (MacLab/400, AD Instruments, Castle Hill, NSW, Australia) and a software application program (Chart, version 3.5, AD Instruments). The concentration of the potent inhalation agent was measured by an anaesthetic gas monitor

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(Capnomac, Datex Instrumentarium, Helsinki, Finland). All procedures were performed at room temperature (26°C) and were repeated three times to verify the reproducibility of the results.

Measurement of NO in gas mixtures containing various concentrations of potent inhalation agents and a fixed concentration of NO

This experiment investigated the concentration effect of potent inhalation agents on NO measurement. NO gas (about 130 ppb) was prepared in a gas sampling bag (Tedlar bag, Tedlar, Osaka, Japan) by mixing a standard gas of NO 670 ppb in nitrogen (N_2) (Taiyo Sanso, Osaka, Japan) and pure N_2 by a gas mixer (GM-3B, Kofloc, Tokyo, Japan). Soda lime (Wako Pure Chemical, Osaka, Japan) was used to absorb nitrogen dioxide during NO gas preparation.[10] Potent inhalation agents at various concentrations were prepared using N_2 as a dilution gas in gas sampling bags (Tedlar bag). Sevoflurane, isoflurane, enflurane and halothane were tested.

The anaesthetic-free reference gas and anaesthetic-containing gas were prepared as follows. Anaesthetic-free reference gas (250 ml) was prepared in a gas sampling bag by mixing 200 ml of NO 130 ppb and 50 ml of N_2. Anaesthetic-containing gas (250 ml) mixtures, to which one of the four potent inhalation agents was added, were prepared by mixing 200 ml of NO 130 ppb and 50 ml of the inhalation agent in various concentrations. The concentrations of NO and potent inhalation agent in each bag were measured simultaneously.

Measurement of NO in gas mixtures containing various concentrations of NO and a fixed concentration of potent inhalation agent

This experiment investigated the concentration effect of NO on NO measurement in the presence of a fixed concentration of a potent inhalation anaesthetic. NO gas mixtures at four different concentrations (25–160 ppb) were prepared in gas sampling bags (Tedlar bag) by mixing NO 670 ppb in N_2 (Taiyo Sanso, Osaka) and pure N_2 with a gas mixer (GM-3B, Kofloc, Tokyo). Halothane, enflurane, isoflurane and sevoflurane were prepared at a fixed concentration using N_2 as a dilution gas in gas sampling bags (Tedlar bag). The anaesthetic-containing gases were prepared by mixing 50 ml of the anaesthetic agent with 200 ml of NO at various concentrations (25–160 ppb). The anaesthetic-free reference gas was prepared by mixing 50 ml of N_2 and 200 ml of NO gas at various concentrations (25–160 ppb). The concentrations of NO and the potent inhalation agent in each bag were measured simultaneously. Changes in the measured NO concentration in the presence of the potent inhalation agent were expressed as the reduction rate using the formula: reduction rate = $(R-M)/R$, where R represents NO concentration in the anaesthetic-free reference gas and M the measured NO concentration in the presence of the potent inhalation agent.

Analysis of chemical reaction of NO with potent inhalation agents

NO-free anaesthetic gases were prepared by bubbling 3 ml of halothane, enflurane, isoflurane or sevoflurane with N_2 at room temperature and atmospheric pressure for 30 min in glass bottles. NO-containing anaesthetic gases were prepared by bubbling 3 ml of each anaesthetic solution with NO 15 ml min^{-1} (3900 ppm in N_2, Nihon Sanso, Japan) in glass bottles for 4 h. The bottles were covered to prevent the effect of light on the chemical reaction and contamination by other gases. The NO-free and NO-bubbled anaesthetic solutions were sampled from the bottles and analysed by a gas chromatograph–mass spectrometer (JMS-DX303, JEOL, Tokyo, Japan) to detect the chemical adducts (NO adducts) between NO and the inhalation agents.

Statistical analysis

The correlation between pairs of variables was examined using the Pearson correlation coefficient. Differences in the slopes of the regression lines were examined by analysis of covariance (ANCOVA) using StatView software (version 5.0, Universal version, Abacus Concepts, Inc., CA, USA). A P value of <0.05 was considered statistically significant

Results

Nitric oxide concentration decreased in the presence of potent inhalation agents and the reduction was dependent on the concentration of the agent. There was a significant correlation ($r^2=0.918$–0.997, $P<0.01$) between the concentration of anaesthetic agent and the measured NO concentration (Fig. 1). The slopes of the linear regression were –2.14 for halothane, –2.37 for enflurane, –1.89 for isoflurane and –2.18 for sevoflurane; there were no significant differences among the slope lines ($P=0.28$).

In the presence of a potent inhalation anaesthetic at a fixed concentration (sevoflurane 5.0%, isoflurane 5.2%, enflurane 4.5% or halothane 6.1%), the rate of reduction in the measured NO concentration increased in proportion to the NO concentration ($r^2=0.909$–0.982, $P<0.01$). The slopes were 0.0066 for halothane, 0.0070 for enflurane, 0.0068 for isoflurane and 0.0066 for sevoflurane; no significant differences in the slope were found among the four inhalation agents ($P=0.99$).

No new compound could be detected in total ion chromatograms (TIC) of gas chromatography–mass spectrometry in the four NO-bubbled anaesthetic agents compared with that of NO-free anaesthetic agents. For example, no peak of NO adduct was recorded in NO-bubbled halothane in the TIC, as shown in Figure 2 Furthermore, no peak of NO adduct could be found when mass chromatography was used.

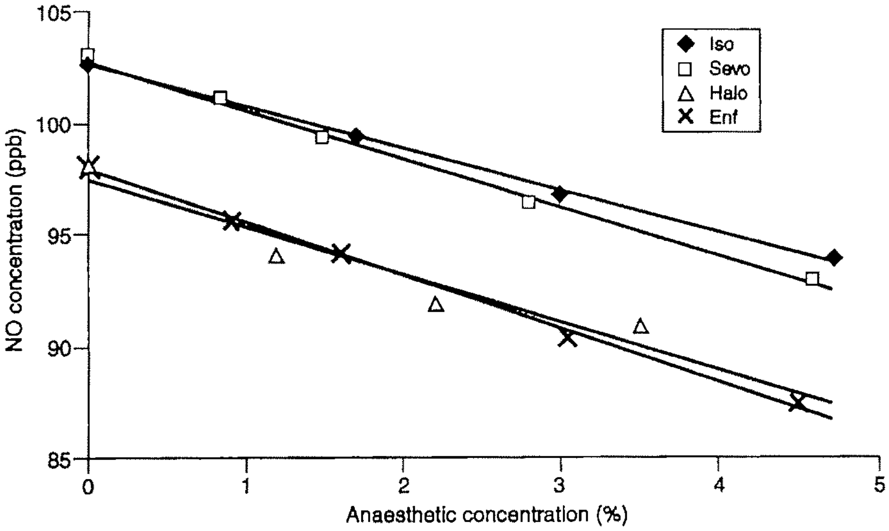

Fig 1 Effect of potent inhalation agents on NO measurement. The measured concentration of NO decreases with increases in the concentration of each anaesthetic agent ($P<0.01$). Iso, isoflurane $y = -1.89x + 102.698$, $R^2 = 0.997$; Sevo, sevoflurane $y = -2.18x + 102.75$, $R^2 = 0.9954$; Hal, halothane $y = -2.14x + 97.45$, $R^2 = 0.918$, Enf, enflurane $y = -2.37x + 97.91$, $R^2 = 0.997$; ppb, parts per billion.

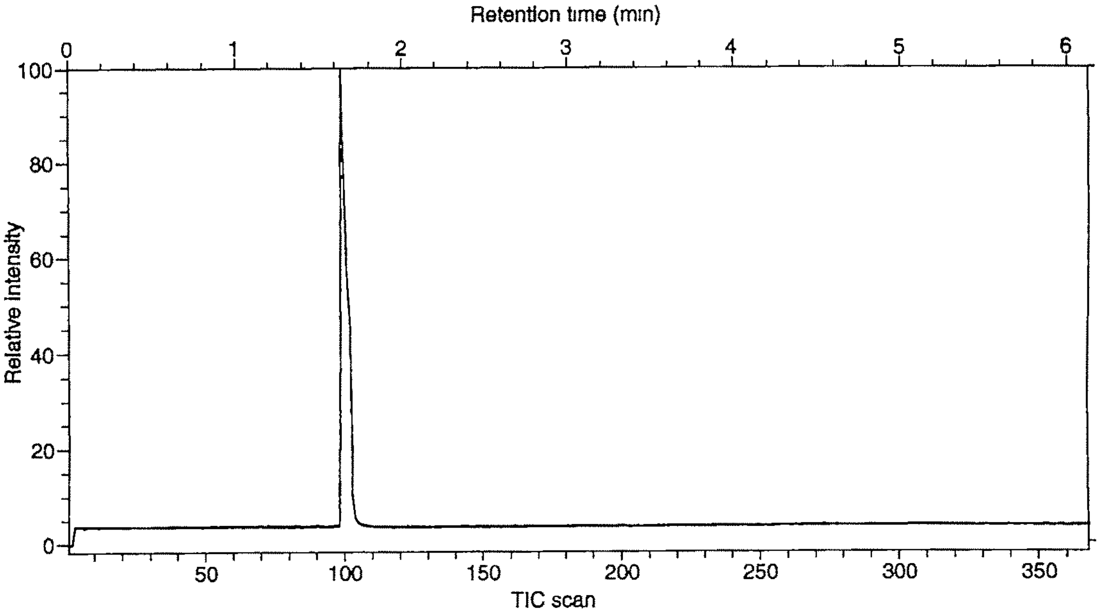

Fig 2 TIC of gas chromatography–mass spectrometry of NO-bubbled halothane. Only one peak, which is identified as halothane, was detected at 1 min 39 s of retention time. No peak of NO adduct was detected.

Discussion

We have shown in this experimental study that the NO concentration measured by chemiluminescence was underestimated in the presence of potent inhalation agents and that this reduction was concentration-dependent.

There are three types of analysers that provide continuous measurement of NO concentration: chemiluminescence analysers; analysers with electrochemical cells; and spectrophotometric gas detectors. The chemiluminescence analyser is commonly used because of its high sensitivity, rapid response time and ease of handling. Our results indicated that four potent inhalation agents (halothane, enflurane, isoflurane and sevoflurane) could interfere with NO measurement by the chemiluminescence method, and that the measured NO concentration was underestimated in a concentration-dependent manner in the presence of increasing concentrations of potent inhalation agent. Furthermore, in the presence of a fixed concentration of anaesthetic agent, the error of estimation increased in proportion to the NO concentration.

Our results indicate that the mechanism by which the potent inhalation agents studied interfere with NO measurement is the same for each of the four agents, as no difference was found between them with regard to the error in the estimated concentration of NO. The NO measurement method used in this study is based on a gas-phase chemiluminescence reaction between NO and ozone to form nitrogen dioxide:

$$NO + O_3 \rightarrow NO_2^* + O_2$$
$$NO_2^* \rightarrow NO_2 + h\nu$$

Emission from electronically excited nitrogen dioxide is in the red and near-infrared region of the spectrum, and is detected by a thermoelectrically cooled, red-sensitive photomultiplier tube. Three mechanisms may affect this process. The first mechanism is based on a chemical reaction; the actual amount of NO may decrease as a result of a reaction before it arrives in the chemiluminescence reaction chamber. For instance, oxygen can react with NO, causing its concentration to be underestimated. It has been reported that chemiluminescence analyser readings can be altered significantly by the presence of oxygen in the ventilator circuit.[8 9] When the oxygen fraction was increased from 0.21 to 1.00, a 4.5 ± 0.3% decrease in NO readings was detected.[8] This is not the explanation for our findings, as oxygen was not used as the carrier gas in this study. Furthermore, no new compound was detected by gas chromatography–mass spectrometry or even by mass chromatography, i.e. there was no direct chemical reaction between the potent inhalation anaesthetic and NO.

The second mechanism is the absorption of emissions. Because emission from electronically excited nitrogen dioxide is in the red and near-infrared region, any other molecules that absorb red and/or near-infrared rays may affect the reading. Potent inhalation agents are known to absorb emissions, including near-infrared emissions, and this mechanism is likely to explain the underestimation of NO concentration in our experiments. However, because at fixed concentrations of potent inhalation agents the NO concentration can be further underestimated as the NO concentration is increased in the target gas, emission absorption by the potent inhalation agent may not be the only mechanism affecting NO measurement.

Another possible mechanism is based on the quenching phenomenon, whereby energy may transfer from the excited nitrogen dioxide to the anaesthetic agent, resulting in a decrease in the emission. To our knowledge, there are no studies that have reported whether potent inhalation anaesthetics quench emission. Further investigation is needed.

In conclusion, NO concentration is underestimated by the chemiluminescence method in the presence of potent inhalation agents. This underestimation may result from emission absorption and/or the quenching phenomenon, but is not attributable to chemical reaction between the potent inhalation agents and NO.

References

1 Hogman M, Stromberg S, Schedin U, *et al.* Nitric oxide from the human respiratory tract efficiently quantified by standardized single breath measurements. *Acta Physiol Scand* 1997; **159**: 345–6

2 Carlin R, Ferrario L, Boyd J, Camporesi E, McGraw D, Hakim T Determinants of nitric oxide in exhaled gas in the isolated rabbit lung. *Am J Respir Crit Care Med* 1997; **155**: 922–7

3 Barnes P, Belvisi M. Nitric oxide and lung disease. *Thorax* 1993; **48**: 1034–43

4 Carlin R, McGraw D, Camporesi E, *et al.* Increased nitric oxide in exhaled gas is an early marker of hypovolemic states. *J Surg Res* 1997; **69**: 362–6

5 Beghetti M, Silkoff P, Caramori M, *et al.* Decreased exhaled nitric oxide may be a marker of cardiopulmonary bypass-induced injury *Ann Thorac Surg* 1998; **66**: 532–4

6 Brett S, Evans T. Measurement of endogenous nitric oxide in the lungs of patients with the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998; **157**. 993–7

7 Sasaki N, Tanifuji Y, Miyasaka K. Accuracy of measuring nitric oxide by the chemiluminescence: effect of measuring chamber pressure *Masui* 1998; **47**: 1007–11

8 Fajardo C, Prokopowich J, Belik J. Inhaled nitric oxide monitoring. *Clin Invest Med* 1995; **18**: 114–21

9 Etches P, Harris M, McKinley R, Finer N. Clinical monitoring of inhaled nitric oxide: comparison of chemiluminescent and electrochemical sensors. *Biomed Instrum Technol* 1995; **29**: 134–40

10 Ishibe Y, Sato T, Hayashi T, Kato N, Hata T. Absorption of nitrogen dioxide and nitric oxide by soda lime. *Br J Anaesth* 1996, **75**: 330–3

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Comparison of exogenous surfactant and positive end-expiratory pressure therapies in a model of human breast milk-induced acute lung injury in rabbits†

C. Chin, B. O'Hare, J. Lerman* and J. Endo

Department of Anaesthesia and the Research Institute, The Hospital For Sick Children and University of Toronto, Toronto, Ontario, Canada

**Corresponding author*

To evaluate surfactant and positive end-expiratory pressure (PEEP) as potential therapies for the acute lung injury after tracheal instillation of 0.8 ml kg^{-1} human breast milk (HBM) acidified to pH 1.8, adult white rabbits were anaesthetized, tracheostomized, ventilated and randomized to (six rabbits per treatment): (i) no treatment after HBM (control); (ii) exogenous Bovine surfactant (100 mg kg^{-1}) 1 h after HBM; (iii) PEEP-pre (0.5 kPa PEEP) before and after HBM; or (iv) PEEP-post (0.5 kPa PEEP) after HBM. A fifth group of six rabbits received no tracheal instillate (no aspirate). The alveolar to arterial oxygen tension gradient (A–aDO_2) and dynamic compliance were measured pre-injury and hourly for 4 h. At post-mortem, the lungs were examined histologically. A–aDO_2 in all four HBM-injured groups increased to a maximum at 1 h post-injury; A–aDO_2 then returned towards the baseline in the surfactant and PEEP-post groups, but remained increased in the PEEP-pre and control groups. Dynamic compliance decreased in all four HBM-injured groups. A–aDO_2 and compliance were unchanged in the no aspirate group. Bronchoalveolar architecture after surfactant therapy was normal. We conclude that surfactant is a more effective therapy for HBM-induced lung injury than either 0.5 kPa PEEP-post or PEEP-pre injury.

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Infants who aspirate human breast milk (HBM) may develop an acute lung injury. In previous studies, we showed that tracheal instillation of 0.8 ml kg^{-1} HBM acidified to a pH of 1.8 in rabbits decreased arterial oxygen tension and lung compliance, activated and recruited neutrophils to the lungs, and produced histological evidence of an acute lung injury.[1–3] The severity of this injury, which persisted for at least 4 h without waning, is consistent with the American–European Consensus Conference on acute respiratory distress syndrome (ARDS) criteria for ARDS.[4] In humans, the mortality from ARDS from all causes including gastric fluid aspiration remains greater than 40%, despite early diagnosis and aggressive treatment with ventilation strategies aimed at improving gas exchange and pulmonary mechanics.[5–8] However, to date, these ventilation strategies have not been evaluated in the setting of HBM-induced lung injury.

Mechanical ventilation, exogenous surfactant and positive end-expiratory pressure (PEEP) are three strategies that have achieved mixed success in treating patients with acute lung injury and ARDS. Mechanical ventilation is frequently required to treat poor gas exchange and lung mechanics as well as a failing cardiopulmonary interaction in patients with ARDS. For the most part, this strategy has been very effective, although there is a growing body of evidence to suggest that aggressive ventilation strategies including large tidal volumes, high-peak-inspired airway pressures and fast respiratory rates may actually exacerbate the lung injury. This may result in an iatrogenic injury termed ventilator-induced lung injury (VILI).[9–13] This iatrogenic injury has been attributed to wide cyclical swings in intrapulmonary shear forces that parallel the swings in airway pressure and tidal volume during aggressive ventilation. In addition to a mechanical component to this injury, recent evidence suggests that overdistention of the small airways and aggressive recruitment of lung units triggers a cytokine response.[14 15] It seems prudent at this time to avoid aggressive ventilation and extreme ventilator settings.

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Abnormalities in both the quantity and quality of surfactant in acid aspiration and ARDS are well documented.[16 17] The aetiology of these abnormalities includes direct epithelial damage, surfactant destruction by cytokines and/or bacteria, inactivation by oedema fluid, and displacement or sequestration of surfactant.[18–21] To address these abnormalities, exogenous surfactant therapy has been used in both animal and human studies of ARDS. In an animal model of acid aspiration, exogenous surfactant improved both gas exchange and lung recoil.[22 23] In ARDS studies in humans, exogenous surfactant therapy consistently improved oxygenation, but did not affect mortality.[24–26] The role of surfactant in HBM-induced lung injury, however, remains to be established.

PEEP has also achieved mixed success as a ventilation adjunct for patients with acute lung injury. In an animal model of acid aspiration, acid damage to the alveolar–capillary membrane increases transmembrane permeability, enabling protein-rich oedema fluid to leak into the alveoli.[18 22] This fluid is thought to contribute to the genesis of atelectasis and ventilation/perfusion mismatch. PEEP re-expands collapsed airways and facilitates the recruitment of lung units, as evidenced by an improvement in oxygenation.[27] However, PEEP has failed to be consistently effective as a ventilation strategy in clinical studies of ARDS.[28] Two possible reasons for variable responses are: (i) the use of large end-inspiratory lung pressures and volumes; and (ii) the timing of the application of PEEP. When PEEP is combined with large tidal volumes, the resultant end-inspiratory pressures and volumes may actually worsen the lung injury, whereas when PEEP is combined with smaller tidal volumes that minimize end-inspiratory pressures and volumes, the injury improves.[29 30] It has also been suggested that the effectiveness of PEEP is determined, in part, by the timing of its application: early application of PEEP may be more effective than late application. Although this concept has not been substantiated in clinical trials,[28] recent evidence suggests that PEEP decreases lung water, and when combined with small tidal volumes may in fact protect small airways from further injury.[31] Whether PEEP is an effective ventilation strategy when it is applied before or after HBM-induced lung injury in rabbits is unknown.

Accordingly, we designed the following prospective, controlled, laboratory investigation to evaluate surfactant and PEEP as adjuvant therapies in the management of acute lung injury induced by intratracheal instillation of HBM in rabbits.

Materials and methods

Surgical preparation

With approval by the institutional animal care committee, pathogen-free adult New Zealand white rabbits (Charles River, St. Constant, Quebec, Canada) weighing 3.2±0.3 kg were studied. The rabbits were fasted overnight for solids and allowed free access to clear fluids up to 4 h before induction of anaesthesia. Each rabbit was premedicated with ketamine 10 mg kg^{-1}, atropine 0.16 mg kg^{-1} and acepromazine 0.2 mg kg^{-1} i.m. After application of electrocardiographic monitoring, anaesthesia was induced with halothane in a nitrous oxide/oxygen gas mixture. Lactated Ringer's solution was infused at a rate of 10 ml kg^{-1} h^{-1} through a 24G cannula in a marginal ear vein. Systemic arterial pressure was monitored continuously via a 24G catheter that was inserted into the common carotid artery under direct vision. Right atrial pressure was monitored continuously via a 5 Fr umbilical catheter that was inserted into the internal jugular vein under direct vision. After subcutaneous infiltration of bupivacaine 1 mg kg^{-1} with epinephrine into the anterior neck caudal to the cricoid cartilage, a surgical tracheostomy was performed between the third and fourth tracheal rings. A 3.5-mm Portex uncuffed tracheal tube was inserted through the stoma to a depth of 3 cm and sealed with a ligature. Bilateral inflation of the lungs was confirmed by observation of symmetrical chest expansion and by auscultation of the thorax. Ventilation was controlled after i.v. administration of pancuronium bromide 0.5 mg kg^{-1}. Paralysis was maintained using a continuous i.v. infusion of pancuronium (0.4 mg kg^{-1} h^{-1}). Intermittent positive pressure ventilation was delivered via a pneumatically operated, time-cycled and volume-limited ventilator (Airshield's Ventimeter Ventilator®, Hatboro, Penn). Anaesthesia was maintained with 1% inspired halothane in humidified oxygen. Rectal body temperature was maintained at 38±1°C using a warming blanket and an overhead infrared radiant heater. Mean arterial pressure was maintained $\geqslant$5.3 kPa (normal $\geqslant$6.67 kPa) and right atrial pressure between 0.27 and 0.67 kPa throughout the study period using intermittent fluid boluses of 5–10 ml kg^{-1} lactated Ringer's solution as necessary. All rabbits were supine throughout the study.

Experimental protocol

After induction of anaesthesia, the tidal volume was adjusted to deliver between 10 and 12 ml kg^{-1}. The respiratory rate was adjusted to produce normocapnia (Pa_{CO_2}4.7–6.0 kPa) before instillation of the HBM. Ventilatory settings were not adjusted subsequently. Cardiotonic or vasoactive drugs were not used in this study. Baseline arterial blood-gas and dynamic compliance measurements were recorded 10 min after stable cardiorespiratory variables. The rabbits were then randomly assigned to one of four treatment groups (six rabbits per group).

1. Control: HBM alone; no additional treatment.
2. Surfactant; 100 mg kg^{-1} bovine lung surfactant (bLES Biochemicals) instilled into the trachea 1 h after HBM.
3. PEEP-pre; 0.5 kPa PEEP before and after HBM instillation.
4. PEEP-post; 0.5 kPa PEEP starting 1 h after HBM.

The pH of the HBM was adjusted to 1.8 with HCl using a Radiometer Copenhagen PHM62b pH meter (Copenhagen, Denmark) that had been calibrated with commercial buffer solutions (pH 1 and pH 4; Fisher Scientific, Nepean, Ontario) before each measurement. The accuracy range of this instrument is ±0.01 pH units.

Following completion of the baseline measurements, 0.8 ml kg^{-1} of acidified HBM was instilled into the trachea through the tracheostomy tube. For rabbits in Group 2, 100 mg ml^{-1} of exogenous surfactant was instilled into the tracheal tube 1 h after HBM. For rabbits in Group 3, 0.5 kPa PEEP was added to the expiratory limb of the ventilator circuit at the start of mechanical ventilation and maintained until the end of the study period. For rabbits in Group 4, 0.5 kPa PEEP was added to the expiratory limb of the ventilator circuit 1 h after instillation of HBM and was maintained until the end of the study.

After completion of the study, six additional rabbits were prepared in the same manner as described above except that no fluid was instilled into the lungs (no aspirate). These rabbits were ventilated for 4 h to control for the effects of mechanical ventilation on the physiological responses (A–aDO_2 and compliance) and histological lung changes.

Blood-gas analysis, peak-inspired pressure and lung volumes were recorded hourly for 4 h after instillation in all rabbits. When the final measurements were completed, the rabbits were killed by administration of pentobarbital 35 mg kg^{-1} followed by KCl 6 mmol kg^{-1} into the right atrium. The lungs were removed en bloc and immersed in 10% formalin until histopathological analysis by a pathologist who was blinded to the treatment. Light microscopic sections from the lungs of each rabbit were stained with haematoxylin and eosin, and examined qualitatively for evidence of alveolar oedema and congestion, atelectasis, particulate matter in the alveolar ducts and white cell infiltration.

Methods of measurement

Arterial blood-gas tensions (carbon dioxide and oxygen) and pH were measured using a Radiometer Copenhagen ABL330 analyser (Copenhagen, Denmark). The alveolar to arterial oxygen tension gradient (A–aDO_2) was calculated as follows: A–aDO_2 = $\{F\text{I}_{O_2}\ [P\text{B} - P\text{H}_2\text{O}] - [Pa_{CO_2}/0.8] - Pa_{O_2}\}$. The arterial and central venous pressures were measured via a calibrated and heparinized saline-filled transducer (Hewlett Packard 78342A, Mississauga, Ontario). The transducers were zeroed at mid-thoracic level. Dynamic compliance was taken as the ratio of the expired tidal volume (measured at the tracheal tube using a precalibrated pneumotachograph connector (Neonatal Volume Monitor-1: Bear Medical Systems, Riverside, CA, USA)) and the peak inspiratory pressure (measured at the distal inspiratory limb of the ventilator circuit). Each expired volume was the average tidal volume of five sequential breaths. Peak inspiratory pressure was measured using a calibrated saline-filled transducer (Hewlett Packard 78342A, Mississauga, Ontario). Compliance was normalized for body weight (measured volume/pressure/kg body weight) to account for any variability in weight among the rabbits.

Data analysis

Data are presented as means (SD). A–aDO_2 and dynamic compliance were analysed using two-factor ANOVA with repeated measures for time on STATISTICA© version 4.1 by StatSoft©, Tulsa, OK, USA on a Macintosh G3, OS 8.5.1. *Post hoc* testing was performed for significant main and interaction effects using the Student–Newman–Keuls test. A value of $P<0.05$ was accepted as statistically significant.

Results

All rabbits completed the study. There were no serious complications observed.

Baseline A–aDO_2 measurements in the five groups were similar (Fig. 1). A–aDO_2 did not change significantly at any time in the no aspirate group. The main effects of treatment and time, and their interaction on A–aDO_2 were all significant ($P<0.0000001$). A–aDO_2 in all four HBM-treated groups worsened by up to fivefold at all post-injury measurements compared to their respective baselines ($P<0.0006$), with the greatest change occurring at 1 h post-injury. At 1 h post-injury, the A–aDO_2 in the PEEP-post group was significantly worse than that in the PEEP-pre group ($P<0.013$). At each hourly measurement after 1 h, the A–aDO_2 measurements in the control and PEEP-pre groups were unchanged. At 2 and 3 h post-injury, A–aDO_2 in the PEEP-post group improved significantly compared to the other three groups (**$P<0.0011$ and ‡$P<0.02$, respectively). At 4 h post-injury, the A–aDO_2 in the surfactant ($P<0.023$) and PEEP-post ($P<0.0011$) groups (40–46.7 kPa) improved significantly compared to those in the control and PEEP-pre groups. The A–aDO_2 in all four HBM-injured groups exceeded that in the no aspiration group at all four post-injury measurements.

Baseline dynamic compliance measurements in the five groups were similar (Fig. 2). Compliance in the no aspirate group did not change during the study period. The main effects of treatment ($P<0.02$) and time ($P<0.0000001$) and their interaction ($P<0.0144$) were significant. Intratracheal HBM significantly decreased dynamic compliance at all four post-injury measurements in the control, surfactant and PEEP-post treatments compared to their respective baselines values ($P<0.0048$), but there was no difference among the three treatments at any time. Compliance in these three groups was significantly less than in the no aspirate group ($P<0.027$) at all times post-injury, except at 1 h PEEP-post and 4 h after surfactant. Compliance measured in the PEEP-pre group post-injury was similar to the baseline, except at 3 and 4 h post-injury when it was significantly less than

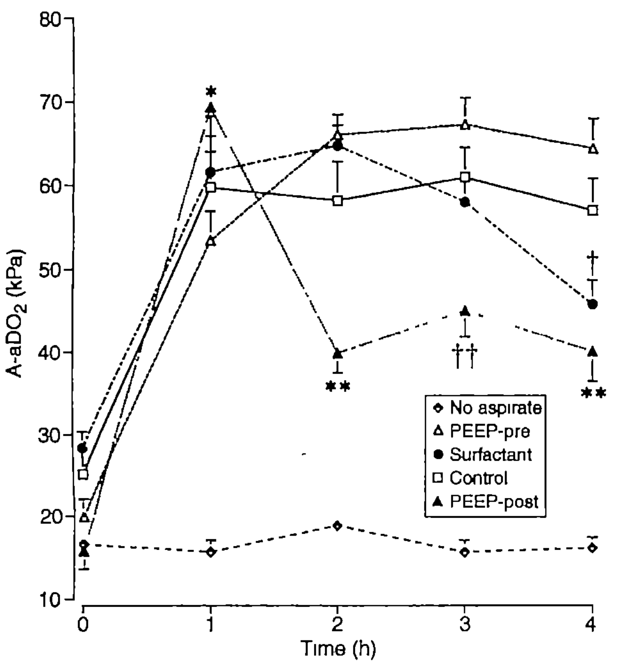

Fig 1 Mean A–aDO$_2$ (SD) before and hourly for 4 h after tracheal instillation of HBM in adult rabbits treated with one of four ventilatory strategies or after instillation of no fluid (no aspirate). Baseline A–aDO$_2$ was similar in all five groups. A–aDO$_2$ in the no aspirate group did not change significantly throughout the study period, but was significantly less than that in the HBM-treated groups at all post-injury measurements. The A–aDO$_2$ in all four HBM-treated groups worsened by up to fivefold after the injury, reaching the worst gradient by 1 h compared to baseline ($P<0.0006$). At 1 h post-injury, the A–aDO$_2$ in the PEEP-post group was significantly worse than that in the PEEP-pre group (*$P<0.013$). A–aDO$_2$ in the control and PEEP-pre groups was unchanged from the 1 h post-injury measurement for the remainder of the study. At 2 and 3 h post-injury, A–aDO$_2$ in the PEEP-post group improved significantly compared to the other three groups (**$P<0.0011$ and ‡$P<0.02$, respectively). At 4 h post-injury, A–aDO$_2$ in the surfactant (†$P<0.023$) and PEEP-post (**$P<0.0011$) groups improved compared to the control and PEEP-pre groups.

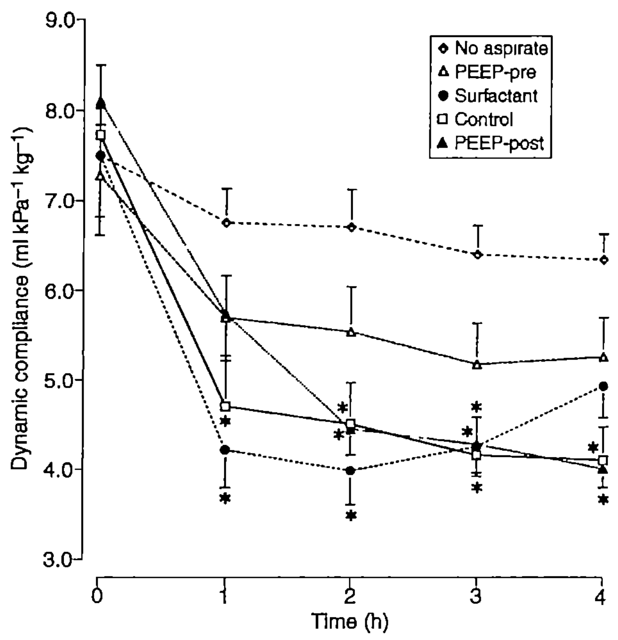

Fig 2 Mean dynamic compliance (SD) before and hourly for 4 h after tracheal instillation of HBM into rabbits treated with one of four ventilatory strategies or after instillation of no fluid (no aspirate). Baseline compliance was similar in all five groups. Compliance in the no aspirate group did not change significantly throughout the study. Compliance decreased at all four hourly post-injury measurements in the control, surfactant and PEEP-post groups compared to their respective baseline values ($P<0.0048$) Compliance in the PEEP-pre group decreased only at 3 and 4 h post-injury ($P<0.023$) compared to baseline. Compliance in the control, surfactant and PEEP-post groups was similar at all four post-injury measurements, but all measurements were significantly less than that in the no aspirate group (*$P<0.027$) at all times except at 1 h post-injury in the PEEP-post group and 4 h post-injury in the surfactant group. PEEP-pre did not differ from the other treatments at any time post-injury.

the baseline ($P<0.023$). Compliance in the PEEP-pre group was intermediate among the other treatments, not differing from them at any time post-injury.

Histological examination of the lungs revealed consistent changes within each group. Histological lung sections are shown (low magnification) from each of the four groups and compared to a lung section of a rabbit ventilated for 4 h but not given HBM. The histology of lungs in the control group showed areas of consolidation and oedema (Fig. 3). In the lungs of rabbits treated with surfactant, histology showed normal bronchoalveolar architecture with evenly spaced alveoli (Fig. 4). In the lungs of rabbits treated with the PEEP-pre, histology showed a blend of both normal inflated alveoli, alveoli filled with transudate and atelectatic alveoli (Fig. 5). In the lungs of rabbits treated with PEEP-post, histology showed areas of consolidation and oedema within alveoli, interspersed with dilated and distended bronchoalveolar spaces (Fig. 6). For comparison, histology of the lungs from the no aspirate group after 4 h of conventional mechanical ventilation showed normal bronchoalveolar architecture (Fig. 7).

Discussion

In the present study, we evaluated exogenous surfactant and 0.5 kPa PEEP as potential therapies for the acute lung injury induced by tracheal instillation of HBM in a rabbit model of aspiration. First, our results confirm that tracheal instillation of 0.8 ml kg^{-1} HBM acidified to a pH of 1.8 in this model induces an acute lung injury that persists for at least 4 h.[1 2 32] Second, both exogenous surfactant 100 mg kg^{-1} and PEEP-post (0.5 kPa) independently attenuate the severity of the A–aDO$_2$; by 2 h in the case of PEEP-post and by 4 h in the case of surfactant, compared to control and PEEP-pre therapies. The salutary effects of surfactant on the A–aDO$_2$ in this model are consistent with recently published data.[32] Qualitative histological examination of the lungs at 4 h after tracheal

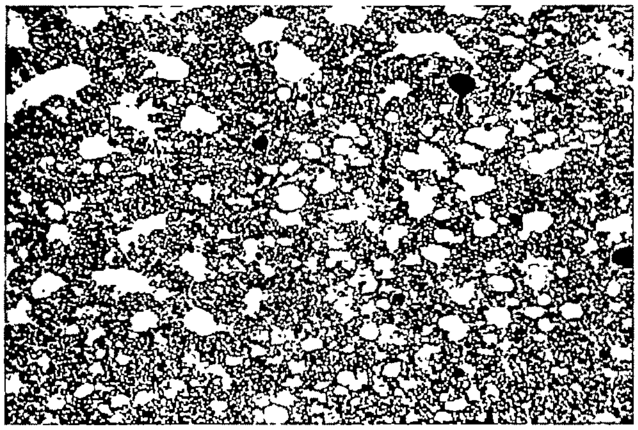

Fig 3 Control group H & E stain of the lungs after tracheal instillation of HBM in rabbits Areas of consolidation are evident within alveoli

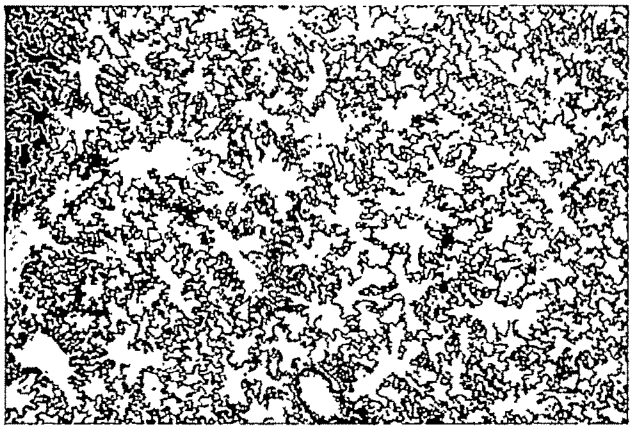

Fig 4 Surfactant-treated lungs H & E stain of the lungs after tracheal instillation of HBM in rabbits and treatment with surfactant Bronchoalveolar architecture appears normal with evenly spaced alveoli on histological examination.

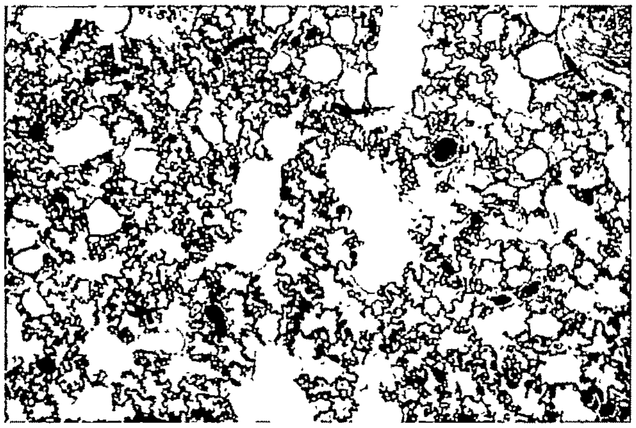

Fig 5 PEEP-pre treated lungs H & E stain of the lungs after tracheal instillation of HBM in rabbits PEEP was applied to the lungs before instillation of the HBM On histological examination, alveolar spaces remain open, although many are filled with pink-stained material that may represent proteinaceous alveolar transudate and/or HBM.

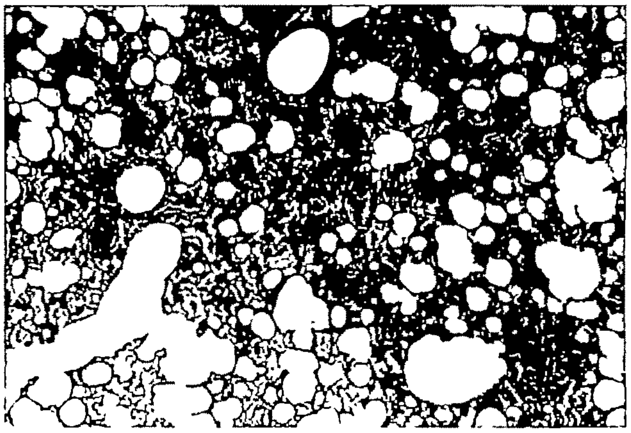

Fig 6 PEEP-post treated lungs. H & E stain of the lungs after tracheal instillation of HBM in rabbits PEEP was applied to the lungs after instillation of the HBM. On histological examination, areas of consolidation are interspersed with areas containing distended bronchoalveolar architecture.

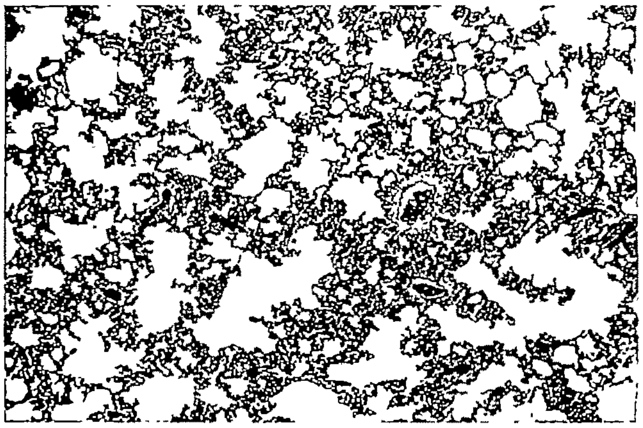

Fig 7 No aspirate. H & E stain of the lungs from healthy rabbits that were ventilated for 4 h. Histological examination of the lungs demonstrates normal bronchoalveolar architecture

instillation of HBM and treatment with surfactant showed normal lung architecture (Fig. 4) similar to that after no aspirate (Fig. 7). In contrast, both the PEEP-pre and PEEP-post showed distorted bronchoalveolar architecture, and congested and collapsed alveoli (Figs 5, 6). These data indicate that tracheal instillation of surfactant 1 h after HBM improves both gas exchange and maintains normal histological architecture of the lungs, whereas 0.5 kPa PEEP-post only improves gas exchange.

In this model of aspiration, the pH and volume of the HBM instilled into the trachea were based on published data. Litman *et al.*[33] measured the pH and volume of gastric fluid aspirated from the stomachs of infants 2 h after breastfeeding. The mean pH of the residual gastric fluid was 2.6 (SD 0.8). If we assume that these pH data were normally distributed, then ⩾84% of all breastfed infants should have, 2 h after feeding, a gastric fluid pH ⩾ 1.8. Accordingly, we acidified the HBM to a pH of 1.8 to reflect the most acidic residual HBM that a majority of infants could aspirate after breastfeeding. The minimum volume of aspirated fluid that leads to severe pneumonitis, 0.8 ml kg^{-1},[34 35] is twice that reported by Roberts and Shirley.[36] In their report, 0.4 ml kg^{-1} was instilled into the airway of a primate, although a careful review of their methodology indicates that they actually instilled the fluid into one bronchus. Instilling 0.4 ml kg^{-1} into one bronchus is equivalent to instilling 0.8 ml kg^{-1} into the trachea, the volume of fluid used in the current study. Although tracheal instillation of a more acidic mixture or larger volume of HBM may have injured the lungs more severely, the lung injury that resulted from tracheal instillation of 0.8 ml kg^{-1} HBM at pH 1.8 reflects that which could occur in a majority of breastfed infants.

Alveolar surfactant may be abnormal after pulmonary aspiration for several reasons. First, published studies in animals demonstrated that pulmonary aspiration of HCl damages the alveolar–capillary membrane.[18 22] The acid damage increases permeability to protein-rich oedema fluid, which inhibits surfactant function.[16 19 20] The reduced effectiveness of surfactant increases the surface tension within alveoli, and therefore, increases transalveolar pressure gradients. These gradients lead to alveolar collapse and ventilation/perfusion mismatch, both of which decrease oxygenation. The gradients also increase the alveolar wall stress, which in turn, fills the alveoli with more transudate and inactivates residual native surfactant. This may be a very important mechanism by which acid aspiration impairs gas exchange and reduces lung compliance. A second possible mechanism for the surfactant abnormalities in HBM-induced lung injury is a direct effect of the constituents of milk on surfactant function.[37] However, this mechanism remains speculative in the absence of substantive evidence. Several studies have established a therapeutic role for exogenous surfactant in acute lung injury and ARDS.[38–40] That oedema-induced inhibition of surfactant depends on the surfactant concentration may explain, in part, how exogenous surfactant replacement therapy attenuates or prevents, in part, the physiological lung changes after HCl acid aspiration[19 20 38 39] and endotoxin-induced lung injury.[40] The improvements in gas exchange and normal alveolar architecture on histological examination after surfactant therapy in the present study are consistent with the results of Nishina *et al.*[32] Together, these two studies support a therapeutic role for 100 mg kg^{-1} surfactant in HBM-induced lung injury.

The effectiveness of PEEP applied 1 h after tracheal instillation of HBM was also evaluated in this study. Because of the dearth of experience with PEEP in this model, we designed this study using 0.5 kPa PEEP as the initial treatment. PEEP-post improved gas exchange but had a minimal effect on the histopathology of the lungs after HBM-induced lung injury. These results are consistent with published data.[27 41 42] Previous studies have suggested that the effectiveness of PEEP in acute lung injury may depend, in part, on the timing of the introduction of PEEP relative to the injury as well as the amount of PEEP applied.[28 31 43] In the present study, we added PEEP 1 h after the injury to provide sufficient time to establish and document the presence of the lung injury. This 1 h time interval between injury and application of PEEP is intermediate between the two extreme times of application of PEEP: immediate application which showed benefit in some studies;[31] and late application of PEEP (2 or 3 h after the injury) which showed no benefit in other studies.[44] Had PEEP been applied immediately after the lung injury in the current study, it is possible that the outcome in the PEEP-post group may have been more favourable. It is also possible that more PEEP might have improved the results, particularly because we did not determine the 'best PEEP'. Evidence from a rabbit model of acid aspiration suggested that a PEEP of 1 kPa did indeed improve oxygenation and compliance above the inflection point on the pressure–volume curve compared with a PEEP of 0.3 kPa, although mortality and histology of the lungs did not differ between the groups.[42] Lastly, combination therapy of surfactant and PEEP was not evaluated in the present study. These two strategies may benefit lung mechanics in a synergistic manner, as recent evidence suggests that in addition to improving lung function, PEEP maintained more of the exogenously administered surfactant in an active form in an animal model of prematurity.[45] On the basis of the findings in this study, further studies are warranted to determine the 'best PEEP' in this model of HBM aspiration, and whether a combination of 'best PEEP' and surfactant is preferable to single strategies for HBM-induced lung injury.

We were somewhat surprised by the severity of the physiological responses after treatment with PEEP-pre. The application of PEEP before the injury should splint open the small airways and improve gas exchange. However, compliance in this group was less than in the control group, and the A–aDO_2 was the largest of all the HBM-injured groups. We hypothesized that the poor physiological responses to PEEP-pre resulted from sub-optimal PEEP and a wider distribution of HBM throughout the lungs. This latter notion is supported by histological findings of pink-stained material in the airspaces throughout the lung.

Recent evidence has suggested that large tidal volumes may lead to VILI.[10 46 47] The probability that VILI will occur seems to increase as the tidal volume increases, with injury occurring at tidal volumes that exceed 18 ml kg^{-1}. In the present study, we used tidal volumes in the range of 10–12 ml kg^{-1} and peak airway pressures between 1.0 and 2.0 kPa, settings that would not be expected to lead to VILI even after 4 h of ventilation. Nonetheless, to control for the effects of mechanical ventilation on the lungs of rabbits without lung injury, we included a 'no aspirate' group in which six rabbits were ventilated mechanically for 4 h. Furthermore, to control for a possible interaction between mechanical ventilation and HBM-induced lung injury,[47] a 'control' group in which HBM was instilled into the trachea and the lungs were ventilated with the standard ventilatory settings was included. In both instances, mechanical ventilation did not adversely affect lung function: in the no aspirate group, physiological and histological markers were unchanged throughout the study; and in the control group, tracheal instillation of HBM produced an acute lung injury that was similar to that reported previously both in severity and duration.[1–3] On the basis of our findings, the modest tidal volumes and peak inspiratory pressures that were used in this model do not appear to predispose to VILI.

We developed this model of acute lung injury after tracheal instillation of HBM to identify those variables that contribute to the severity of the lung injury as well as effective therapeutic modalities. This model has proved to be reliable and stable.[9–12 32] The stability of this model together with the absence of eosinophilia on histological examination of the lungs and the peripheral blood smear, and the absence of progressive cardio-respiratory collapse suggest that this lung injury is not an immunologically mediated cross-species response to a foreign material, specifically HBM, within the lungs of rabbits.

Conclusions

We conclude that exogenous surfactant therapy improves gas exchange and compliance as well as maintains normal bronchoalveolar architecture in a rabbit model of acute lung injury induced by tracheal instillation of HBM. PEEP applied 1 h post-HBM improves oxygenation but does not affect the histology of the lung parenchyma. PEEP-pre is the least effective of the three treatments.

Acknowledgement

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References

1 O'Hare BP, Lerman J, Endo J, Cutz E. Acute lung injury after instillation of human breast milk or infant formula into rabbits' lungs. *Anesthesiology* 1996; **84**: 1386–91

2 O'Hare B, Chin C, Lerman J, Endo J, Cutz E Acute lung injury after instillation of human breast milk into rabbits lungs: effects of pH and gastric juice. *Anesthesiology* 1999; **90**: 1112–8

3 Chin C, Lerman J, Endo J, Cutz E. Physiologic responses to tracheal instillation of soya, enfalac® or human breast milk in rabbits. *Can J Anaesth* 1999; **46**: 282–6

4 Bernard GR, Artigas A, Brigham KL, *et al.* The American–European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; **149**: 818–24

5 Suchyta MR, Clemmer TP, Elliott CG, Orme Jr. JF, Weaver LK. The adult respiratory distress syndrome: a report of survival and modifying factors. *Chest* 1992; **101**: 1074–9

6 Milberg JA, Davis DR, Steinberg KP, Hudson LD. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983–1993. *JAMA* 1995; **273**: 306–9

7 Abel SJC, Finney SJ, Brett SJ, Keogh BF, Morgan CJ, Evans TW. Reduced mortality in association with the acute respiratory distress syndrome (ARDS). *Thorax* 1998; **53**: 292–4

8 Luhr OR, Antonsen K, Karlsson M, *et al.* Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. *Am J Respir Crit Care Med* 1999; **159**: 1849–61

9 Parker JC, Hernandez LA, Peevy KJ. Mechanisms of ventilator-induced lung injury. *Crit Care Med* 1993; **21**: 131–43

10 Corbridge TC, Wood LD, Crawford GP, Chudoba MJ, Yanas J, Sznajder JI. Adverse effects of large tidal volume and low PEEP in canine acid aspiration. *Am Rev Respir Dis* 1990; **142**: 311–5

11 Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema: respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis* 1988; **137**: 1159–64

12 Tsuno K, Prato P, Kolobow T. Acute lung injury from mechanical ventilation at moderately high airway pressures. *J Appl Physiol* 1990; **69**: 956–61

13 Muscedere JG, Mullen JBM, Gan K, Slutsky AS. Tidal ventilation at low pressures can augment lung injury. *Am J Respir Crit Care Med* 1994; **149**: 1327–34

14 Ranieri VM, Suter PM, Tortorella C, *et al.* Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome. a randomized controlled trial. *JAMA* 1999; **282**: 54–61

15 Dunn I, Pugin J. Mechanical ventilation of various human lung cells *in vitro*: identification of the macrophage as the main producer of inflammatory mediators. *Chest* 1999; **116**. 95S–6S

16 Lewis JF, Jobe AH. Surfactant and the adult respiratory distress syndrome. *Am Rev Respir Dis* 1993; **147**: 218–33

17 Gregory TJ, Longmore WJ, Moxley MA, *et al.* Surfactant chemical composition and biophysical activity in acute respiratory distress syndrome. *J Clin Invest* 1991; **88**: 1976–81

18 Greenfield LJ, Singleton RP, McCaffee DR, Coalson JJ. Pulmonary effects of experimental graded aspiration of hydrochloric acid. *Ann Surg* 1969; **170**: 74–86

19 Holm BA, Enhorning G, Notter RH. A biophysical mechanism by which plasma proteins inhibit lung surfactant activity. *Chem Phys Lipids* 1988; **49**. 49–55

20 Seeger W. Stohr G, Wolf HRD, Neuhof H. Alteration of surfactant function due to protein leakage: special interaction with fibrin monomer. *J Appl Physiol* 1985; **58**: 326–38

21 Winn R, Stothert J, Nadir B, Hildebrandt J. Lung mechanics following aspiration of 0.1 hydrochloric acid. *J Appl Physiol* 1983; **55**: 1051–6

22 Kobayashi T, Ganzuka M, Tanigushi J, *et al.* Lung lavage and surfactant replacement for hydrochloric acid aspiration in rabbits. *Acta Anaesth Scand* 1990; **34**: 216–21

23 Lamm WJE, Albert RK. Surfactant replacement improves lung recoil in rabbit lungs after acid aspiration *Am Rev Respir Dis* 1990; **142**: 1279–83

24 Anzueto A, Baughman RP, Guntupalli KK, *et al.* Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. Exosurf Acute Respiratory Distress Syndrome Sepsis Study Group. *N Engl J Med* 1996; **334**: 1417–21

25 Gregory TJ, Steinberg KP, Spragg R, *et al.* Bovine surfactant therapy for patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 1997; **155**: 1309–15

26 Lopez-Herce J, de Lucas N, Carrillo A, Bustinza A, Moral R. Surfactant treatment for acute respiratory distress syndrome. *Arch Dis Child* 1999; **80**: 248–52

27 Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967; **2**: 319–23

28 Pepe PE, Hudson LD, Carrico JC. Early application of positive end-expiratory pressure in patients at risk for the adult respiratory-distress syndrome. *N Engl J Med* 1984; **311**: 281–6

29 Dreyfuss D, Saumon G. Ventilator induced lung injury. Lessons from experimental studies. *Am J Respir Crit Care Med* 1998; **157**: 294–323

30 Rossi N, Kolobow T, Aprigliano M, Tsuno K, Giacomini M.

intratracheal pulmonary ventilation at low airway pressures in a ventilator-induced model of acute respiratory failure improves lung function and survival. *Chest* 1998; **114**: 1147–57

31 Ruiz-Bailén M, Fernandez-Mondejar E, Hurtado-Ruiz B, *et al.* Immediate application of positive-end expiratory pressure is more effective than delayed positive-end expiratory pressure to reduce extravascular lung water. *Crit Care Med* 1999; **27**: 380–4

32 Nishina K, Mikaewa K, Takao Y, Maekawa N, Obara H. Effects of pulmonary surfactant on acute lung injury after instillation of human breast milk or infant formula into rabbits' lungs. *Anesthesiology* 1999; **91**: 240–52

33 Litman RS, Wu CL, Quinlivan JK. Gastric volume and pH in infants fed clear liquids and breast milk prior to surgery. *Anesth Analg* 1994; **79**: 482–5

34 James CF, Modell JH, Gibbs CP, Kuck EJ, Ruiz BC. Pulmonary aspiration – effects of volume and pH in the rat. *Anesth Analg* 1984; **63**: 665–8

35 Raidoo DM, Rocke DA, Brock-Utne JG, Marszalek A, Engelbrecht HE. Critical volume for pulmonary acid aspiration: reappraisal in a primate model. *Br J Anaesth* 1990; **65**: 248–50

36 Roberts RB, Shirley MA. Antacid therapy in obstetrics (letter). *Anesthesiology* 1980; **53**: 83

37 Fuchimukai T, Fujiwara T, Takahashi A, Enhorning G. Artificial pulmonary surfactant inhibited by proteins. *J Appl Physiol* 1987; **62**: 429–37

38 Eijking EP, Gommers D, So KL, *et al.* Prevention of respiratory failure after hydrochloric acid aspiration by intratracheal surfactant instillation in rats. *Anesth Analg* 1993; **76**: 472–7

39 Trohmaier W, Reidl H, Schlag G. Studies of the potential role of semisynthetic surfactant preparation in an experimental aspiration trauma in rabbits. *Exper Lung Res* 1990; **16**: 101–10

40 Lutz C, Carney D, Finck C, *et al.* Aerosolized surfactant improves pulmonary function in endotoxin-induced lung injury. *Am J Resp Crit Care Med* 1998; **158**: 840–5

41 Luce JM, Robertson HT, Huang T, *et al.* The effects of expiratory positive airway pressure on the resolution of oleic acid-induced lung injury in dogs. *Am Rev Respir Dis* 1982; **125**: 716–22

42 Sohma A, Brampton WJ, Dunnill MS, Sykes MK. Effect of ventilation and positive end-expiratory pressure on the development of lung damage in experimental acid aspiration pneumonia in the rabbit. *Intens Care Med* 1993; **18**: 112–7

43 Weigelt JA, Mitchell RA, Snyder WH III. Early positive end-expiratory pressure in the adult respiratory distress syndrome. *Arch Surg* 1979; **114**: 497–501

44 Malo J, Ali J, Wood LDH. How does positive end-expiratory pressure reduce intrapulmonary shunt in canine pulmonary edema? *J Appl Physiol* 1984; **57**: 1002–10

45 Michna J, Jobe AH, Ikegami M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. *Am J Respir Crit Care Med* 1999; **160**: 634–9

46 Bowton DL, Kong DL. High tidal volume ventilation produces increased lung water in oleic acid-injured rabbit lungs. *Crit Care Med* 1989; **17**: 908–11

47 Dreyfuss D, Soler P, Saumon G. Mechanical ventilation-induced pulmonary edema: interactions with previous lung alterations. *Am J Respir Crit Care Med* 1995; **151**: 1568–75

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Fentanyl reduces infarction but not stunning via δ-opioid receptors and protein kinase C in rats

R. Kato* and P. Foëx

Nuffield Department of Anaesthetics, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, UK

**Corresponding author*

Langendorff rat hearts were used (i) to examine whether fentanyl reduces stunning, infarction or both, and (ii) to investigate if this protection is mediated by δ-opioid receptors and/or protein kinase C (PKC). In the stunning study, hearts were subjected to global ischaemia (20 min) and reperfusion. This did not produce infarction. Postischaemic mechanical function was measured in hearts treated with or without fentanyl (740 nM). Fentanyl did not affect postischaemic mechanical function. In the infarction study, the left anterior descending coronary artery was occluded for 35 min and infarct size was assessed by triphenyltetrazolium chloride staining. Hearts in the control group exhibited an infarct zone/area at risk (I/R) of 39 (SEM 5)%, whereas the I/R for the fentanyl group was 13 (2)%. When the hearts were treated with a δ-opioid receptor antagonist (naltrindole 1 nM) or a PKC inhibitor (chelerythrine 2 μM), the effect of fentanyl was abolished, with I/R of 37 (1) and 36 (2)% respectively. In our model, we conclude that fentanyl protects against infarction but not against stunning, and that the limitation of ischaemic injury is mediated by both δ-opioid receptors and PKC.

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Keywords: analgesics, opioids, fentanyl; heart, myocardial ischaemia; enzymes, protein kinase C; receptors, opioid

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The last decades have witnessed a large increase in the number of surgical patients with ischaemic heart disease. Anaesthetists very often treat patients with coronary artery disease and make strenuous efforts to minimize perioperative myocardial ischaemia. More than 10 years ago it was reported that halothane and isoflurane protected against myocardial stunning. Additional evidence that inhalational anaesthetics diminish myocardial injury following ischaemia has been reviewed recently by Ross and Foëx.[1] Moreover, morphine has been found to limit infarct size,[2–4] hence there is increasing interest in opioids as cardioprotective agents.

Ischaemic preconditioning is another mechanism by which the myocardium can be protected against ischaemic injury. Ischaemic preconditioning describes the protection against subsequent damage caused by prolonged ischaemia, conferred by brief periods of ischaemia.[5–7] This protective state lasts 1–3 h and has been demonstrated in a wide variety of animal species and in humans.[5 6] Activation of protein kinase C (PKC) seems to play a major role in ischaemic preconditioning.[6 7] PKC reportedly opens K_{ATP} channels, whose central role in ischaemic preconditioning has been generally accepted.[6 7] PKC is stimulated by opioid receptor agonists as well as adenosine A_1, bradykinin and noradrenaline receptor agonists and free radicals.[6 7] All these substances are endogenously released in the myocardium by ischaemia and, therefore, are putative mediators of ischaemic preconditioning.[6 7]

In a previous report, we demonstrated that fentanyl alleviated postischaemic ventricular dysfunction and that this cardioprotective effect was mediated by opioid receptors and K_{ATP} channels.[8] We speculated that the cellular signal conferring the beneficial effect was passed from opioid receptors to K_{ATP} channels through the activation of PKC. Indeed, bradykinin,[9] adenosine,[10 11] endothelin[12] and noradrenaline,[13] which share common signal transduction pathways with opioids, diminish myocardial injury after ischaemia. Of further importance, this reduction in ischaemic damage is blocked by PKC inhibitors[9 10 12 13] or K_{ATP} channel blockers.[11 12] However, our previous study did not directly examine the role of PKC in the protection conferred by fentanyl.

Although fentanyl has a preferential affinity for μ-opioid receptors, it also interacts with δ- and κ-receptors.[14] Of the three major opioid receptors, δ- and κ- but not μ-receptors are expressed in the rat myocardium.[15] κ-Agonists have been reported to be arrhythmogenic and to worsen haemodynamics in ischaemia.[16 17] In contrast, δ-opioid receptors seem to be involved with myocardial protection against ischaemic damage.[3 18–21] This raises our second question,

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of whether the attenuation of postischaemic dysfunction by fentanyl resulted from δ-opioid receptor stimulation.

The third question left unsolved was whether fentanyl protects against stunning or infarction, as we assessed left ventricular mechanical function. This can reflect the degree of both types of ischaemic injury, and we used a period of global ischaemia that lasted 30 min, which may result in a mixture of both types of damage.[22]

Therefore, we decided to examine (i) if fentanyl reduces stunning and/or infarction, and (ii) if the protection given by fentanyl is mediated by PKC and/or δ-opioid receptors.

Methods

The study was performed in accordance with the United Kingdom Animal Act (Scientific Procedures) 1986 (Home Office Project Licence number PPL 30/1496).

Preparation of rat hearts

The methods used have been described in detail elsewhere.[8] Adult male Wistar rats (325–400 g) were anaesthetized with intraperitoneal pentobarbitone 60 mg kg^{-1} and heparin 200 IU was administered. The hearts were rapidly excised, arrested in ice-cooled Krebs–Henseleit (KH) buffer, and perfused with KH solution by the Langendorff method. The perfusion pressure was set at 100 cm H_2O and kept constant. A polyvinyl balloon filled with KH solution was inserted through the left atrium into the left ventricle and connected to a pressure transducer. A small thermistor (T200K, Digitron Instruments, Hertford, UK) was placed in the left ventricle and the heart temperature was kept at 37°C during the procedure. All hearts were paced at a fixed rate of 300 bpm. The volume of the balloon was adjusted to achieve an end-diastolic pressure (EDP) between 5 and 10 mm Hg, which was maintained throughout the procedure. In the infarction study, a 3/0 silk suture (W598, Mersilk, Ethicon, Edinburgh, UK) was passed around the main branch of the left anterior descending coronary artery (LAD) to make a snare.

Experimental design

Figure 1 summarizes the procedure.

Stunning study

Groups stn-Con (n=9) received no drug. Fentanyl was administered to the perfusate in group stn-Fen (n=9) and remained in the perfusate for the rest of the procedure. After the drug incubation period, the aortic flow was stopped and global ischaemia induced. Ventricular pacing was stopped during ischaemia. After 20 min, aortic flow was reintroduced and continued for 120 min. Pacing was reintroduced 8 min into reperfusion and continued until the end of the procedure.

Infarction study

The hearts were allocated to one of six groups depending upon the chemicals added to the perfusate. Group inf-Con was treated with no drug (n=6), group inf-Fen with fentanyl (n=6), group inf-Nlt with the selective δ-opioid receptor antagonist naltrindole (n=5), group inf-Fen+Nlt with fentanyl and naltrindole (n=5), group inf-Che with the PKC inhibitor chelerythrine (n=5) and group inf-Fen+Che with fentanyl and chelerythrine (n=5). Regional ischaemia was induced by tightening the snare around the coronary artery. After an ischaemic period of 35 min, the snare was loosened and the heart was reperfused. Pacing was maintained throughout the procedure.

In both studies, haemodynamic measurements were taken after stabilization (pre-drug), before ischaemia (pre-ischaemia) and at several points during reperfusion. Measurements included developed pressure (DP), EDP, maximum positive and minimum negative derivative of left ventricular pressure ($+\mathrm{d}P/\mathrm{d}t_{max}$ and $-\mathrm{d}P/\mathrm{d}t_{min}$ respectively) and coronary flow (CF). Details of haemodynamic data collection have been published elsewhere.[8] At the end of perfusion, infarct size was measured using the triphenyltetrazolium chloride (TTC) staining method (see below). The concentrations of the drugs were fentanyl 740 nM (Janssen-Cilag, Buckinghamshire, UK), naltrindole 1 nM (Research Biochemicals International, MA, USA) and chelerythrine 2 μM (Research Biochemicals International).

Evaluation of infarct area

Stunning study

The heart was frozen and sliced into cross-sectional pieces just over 1 mm thick. The pieces were incubated in 1% TTC (Sigma Chemical Co., Dorset, UK) in 0.1 M phosphate buffer (pH=7.4) at 37°C for 20–30 min. This was used to distinguish unstained (grey) infarct and stained (red) non-infarct zones. The slices were immersed in 10% formalin in saline for 1–2 days. The slices were sandwiched between transparent plates to a thickness of 1 mm. The image of the heart slices were traced on a transparent sheet. Infarct and non-infarct areas were determined by planimetry using SigmaScan (Jandel Corporation, CA, USA).

Infarction study

The LAD occluder was retightened at the end of reperfusion and 0.125% Evans blue in saline was injected into the heart through the aorta for visualization of the non-ischaemic zone. Hearts were then sliced and stained in the same way as in the stunning study. Each non-ischaemic, risk (ischaemic but not infarct) or infarct area was determined by planimetry.

Statistics

All values are expressed as mean (SEM). Differences in haemodynamic indices between groups at various time points were compared using two-way analysis of variance (ANOVA) for treatment and time with repeated measures on a time factor. The comparison of infarct area/area at risk and area at risk was performed by one-way ANOVA combined with Bonferroni's test. Statistical significance was assumed at the P<0.05 level.

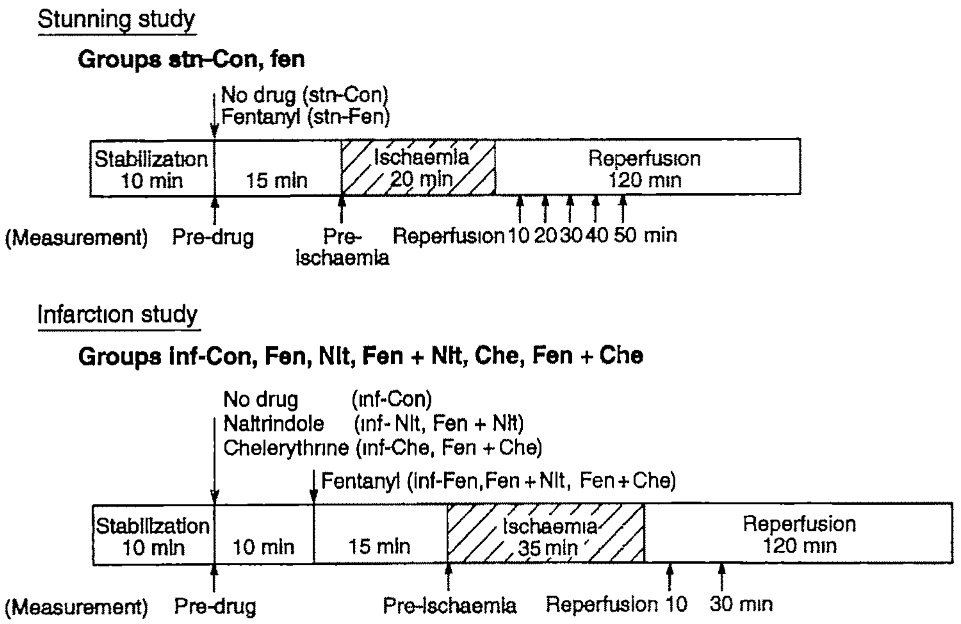

Fig 1 Procedure of the experiments.

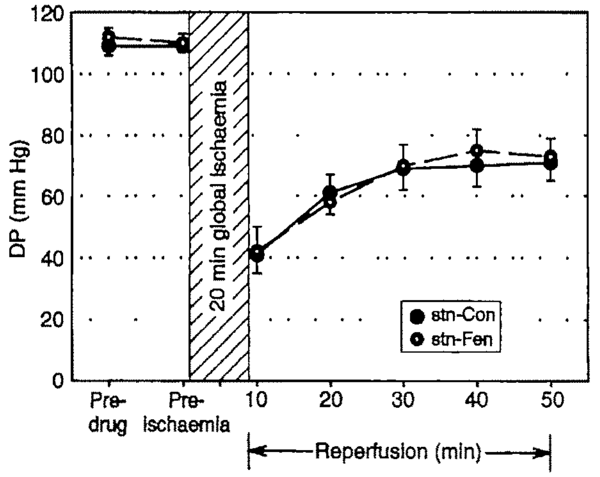

Fig 2 Recovery of developed pressure (DP) in the stunning study Results are mean (SEM). No significant difference was found between the groups. stn=stunning, Con=control; Fen=fentanyl.

Results

Stunning study

The indices of mechanical function obtained for DP, PSP, EDP, $+dP/dt_{max}$, $-dP/dt_{min}$ and CF are shown in Figure 2 and Table 1. Groups stn-Con and stn-Fen showed similar recovery profiles and there were no significant differences in any index at any time. No unstained (infarct) area was detected by TTC in any hearts.

Infarction study

Table 2 illustrates haemodynamic parameters. No significant difference was found between the groups. Infarct area/area at risk (I/R) was 39 (5)% in the control group, whereas fentanyl significantly reduced I/R to 13 (2)% ($P<0.01$) (Fig. 3). Naltrindole and chelerythrine alone did not affect I/R (39 (2)% in inf-Nlt, 35 (2)% in inf-Che). When fentanyl was given with either naltrindole or chelerythrine, the extent of infarction did not differ from control (I/R was 37 (1)% for group inf-Fen+Nlt and 36 (2)% for group Fen+Che). The area at risk (mm^2) was 212 (12) in group inf-Con, 214 (8) in group Fen and 223 (7) in group Nlt, and 217 (8) in group Fen+Nlt, 207 (8) in group Che and 214 (8) in group Fen+Che (not significant).

Discussion

The present study shows that fentanyl reduced the extent of infarction. A similar effect has been demonstrated for morphine. In response to a LAD occlusion lasting 30 min in isolated rabbit hearts, morphine decreased infarct/area at risk from 32 to 9%.[4] Morphine also reduced necrosis in hearts *in vivo* [2–4] and in isolated ventricular myocytes;[21] this effect was abolished by an opioid receptor antagonist.[2 4 21] The attenuation of infarct area by fentanyl is consistent with these findings.

This cardioprotection produced by fentanyl was eliminated by the selective δ-opioid receptor antagonist naltrindole. Schultz and colleagues showed that a δ_1-opioid receptor agonist limited infarct size,[19] and that ischaemic preconditioning was mediated by δ- but not μ- or κ-receptors.[3 20] In addition, morphine-induced protection was demonstrated to result from δ-receptor activation.[3 21] It should be noted that these studies on opioid subtypes have been conducted in rats, a species in which μ-receptors have not been identified.[15] However, in other species, μ-receptors may be identified in the myocardium, and the activation of μ-receptors could affect the degree of ischaemic injury.

Table 1 Haemodynamic indices before and after ischaemia in the stunning study. Results are mean (SEM). There were no differences between the two groups in any index at any measurement point. DP=developed pressure; EDP=end-diastolic pressure, $+dP/dt_{max}$=maximum positive derivative of left ventricular pressure; $-dP/dt_{min}$=minimum positive derivative of left ventricular pressure; CF=coronary flow; stn=stunning; Con=control, Fen=fentanyl

	Before drug	**Before ischaemia**	**Reperfusion (min)**				
			10	**20**	**30**	**40**	**50**
DP (mm Hg)							
stn-Con	109 (3)	109 (2)	41 (6)	61 (7)	69 (7)	70 (7)	71 (5)
stn-Fen	112 (3)	110 (3)	42 (8)	58 (9)	70 (7)	75 (7)	73 (6)
EDP (mm Hg)							
stn-Con	6 (0)	6 (0)	55 (6)	40 (5)	35 (5)	33 (5)	33 (4)
stn-Fen	5 (0)	5 (0)	55 (7)	40 (5)	34 (5)	32 (4)	32 (4)
$+dP/dt$max (mm Hg s^{-1})							
stn-Con	2782 (77)	2857 (61)	861 (177)	1489 (227)	1778 (238)	1898 (214)	1922 (201)
stn-Fen	2937 (90)	2989 (83)	932 (227)	1500 (242)	1929 (227)	2151 (207)	2176 (176)
$-dP/dt$min (mm Hg s^{-1})							
stn-Con	2203 (126)	2157 (73)	592 (147)	1167 (179)	1342 (180)	1409 (166)	1408 (157)
stn-Fen	2112 (57)	2134 (57)	768 (165)	1148 (175)	1391 (147)	1481 (145)	1463 (125)
CF (ml min^{-1})							
stn-Con	18 (1)	17 (1)	13 (1)	14 (1)	14 (0)	14 (0)	13 (0)
stn-Fen	17 (1)	17 (1)	13 (1)	14 (1)	14 (1)	13 (1)	13 (1)

Table 2 Haemodynamic indices in the infarction study. Results are mean (SEM). No differences were found between groups DP=developed pressure, EDP=end-diastolic pressure; CF=coronary flow; inf=infarction; Con=control; Fen=fentanyl, Nlt=naltrindole, Che=chelerythrine

	Before drug	**Before ischaemia**	**Ischaemia (min)**		**Reperfusion (min)**	
			5	**35**	**10**	**30**
DP (mm Hg)						
inf-Con	112 (6)	109 (8)	35 (3)	56 (5)	90 (3)	83 (7)
inf-Fen	111 (5)	107 (5)	37 (3)	57 (4)	86 (1)	77 (8)
inf-Nlt	112 (3)	108 (2)	42 (2)	58 (1)	90 (2)	87 (4)
inf-Fen+Nlt	108 (5)	103 (2)	42 (4)	59 (3)	86 (2)	81 (2)
inf-Che	112 (5)	109 (7)	41 (5)	58 (5)	92 (7)	92 (7)
inf-Fen+Che	108 (4)	105 (5)	47 (3)	63 (4)	87 (6)	84 (4)
EDP (mm Hg)						
inf-Con	6 (0)	5 (1)	3 (0)	4 (1)	10 (2)	9 (2)
inf-Fen	5 (0)	5 (1)	4 (0)	3 (0)	7 (1)	7 (1)
inf-Nlt	5 (1)	6 (1)	4 (1)	5 (1)	11 (2)	9 (2)
inf-Fen+Nlt	5 (1)	5 (1)	4 (0)	5 (1)	13 (3)	10 (2)
inf-Che	6 (0)	6 (0)	5 (1)	5 (1)	9 (1)	7 (1)
inf-Fen+Che	6 (1)	5 (0)	4 (0)	4 (0)	8 (1)	6 (1)
CF (ml min^{-1})						
inf-Con	19 (0)	18 (1)	8 (1)	8 (1)	17 (1)	17 (1)
inf-Fen	18 (1)	19 (2)	9 (1)	10 (1)	20 (1)	17 (1)
inf-Nlt	18 (1)	17 (0)	8 (1)	9 (1)	20 (2)	18 (2)
inf-Fen+Nlt	19 (1)	18 (1)	8 (1)	10 (1)	19 (1)	18 (1)
inf-Che	18 (0)	18 (1)	9 (1)	10 (1)	19 (1)	18 (1)
inf-Fen+Che	18 (1)	17 (1)	9 (1)	9 (1)	18 (1)	17 (1)

PKC transfers γ-phosphate from ATP to hydroxyl groups of serine/threonine residues in proteins. In the cardiac myocytes, this phosphorylation controls the function of many cellular effectors, and hence regulates various events, such as contraction and cell growth.[23] Consistent with our hypothesis, the PKC inhibitor chelerythrine eliminated the cardioprotective effect of fentanyl, resulting in increased infarct area. Miki and colleagues also showed in rabbits that chelerythrine abolished the infarct-limiting effect of morphine.[4] Our study also suggests that opioids reduce infarct size through PKC-linked mechanisms. PKC and K_{ATP} channels are signalling effectors shown to be central to ischaemic preconditioning.[6 7] In our previous study, we demonstrated that fentanyl elicits myocardial protection via opioid receptors and K_{ATP} channels. Taking into account previous findings, the present study strongly supports the PKC hypothesis for the protective mechanism of fentanyl; that is, the signal from fentanyl is passed to δ-opioid receptors, PKC and then K_{ATP} channels in the myocardium.

However, the PKC hypothesis remains somewhat controversial. Firstly, the link between δ-opioid receptors and PKC has not been characterized directly in the myocardium. In rat myocytes, Ventura and colleagues demonstrated that δ-receptor stimulation increased the level of inositol 1,4,5-triphosphate.[24] PKC-coupled receptors generally induce phosphoinositide turnover, leading to the production of

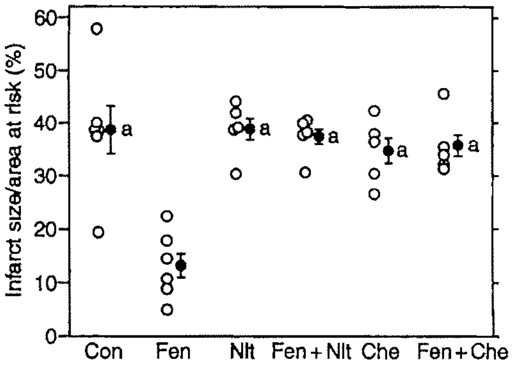

Fig 3 Infarct area/area at risk (I/R) after 35 min regional ischaemia. Open and closed circles represent individual animal I/R and group mean (SEM) respectively. a=$P<0.01$ compared with the group receiving fentanyl alone. Con=control, Fen=fentanyl; Nlt=naltrindole; Che=chelerythrine

inositol 1,4,5-triphosphate and diacylglycerol; the latter activates PKC directly.[23 25] In glial cells, however, it is widely accepted that δ-opioid receptor agonists activate PKC[26 27], and this could be extrapolated to the myocardium.

Secondly, some authors have taken issue with a number of previous studies which support PKC as a major contributor to preconditioning.[23 28] They argue that what was considered as the effects of PKC agonists or antagonists could have been caused by other kinases. Most of the reports were based on the use of various PKC agonists and antagonists, many of which may not be specific for PKC and may affect other protein kinases. We also used a pharmacological method in this study, and therefore our findings are not free from this criticism. There are currently no reliable standard techniques; thus, the controversy over PKC will not be resolved conclusively until selective PKC inhibitors have been developed.[23 25]

PKC inhibitors have been reported recently to be cardioprotective against ischaemic injury at relatively low doses.[29 30] Chelerythrine 1 μM alleviated ischaemic injury in rats according to Lundmark and colleagues.[30] In contrast, Bugge and colleagues have reported that 2 μM chelerythrine blocked the infarct-reducing effect of ischaemic preconditioning,[31] bradykinin[9] and endothelin[12] without showing protective effects. Our finding is in agreement with the studies by Bugge and colleagues.[9 12 31]

It is generally agreed that K_{ATP} channels, which are primed by PKC, function as pivotal effectors in ischaemic and pharmacological preconditioning.[6 7] There are two kinds of K_{ATP} channels in the myocardium: sarcolemmal and mitochondrial K_{ATP} channels. Recent studies suggest that mitochondrial K_{ATP} mediate cardioprotection.[32] However, the nature of more distal effectors is currently poorly understood, and remains a controversial issue in the PKC hypothesis.

As we used a whole-heart model, the myocardium is not the only fentanyl-sensitive target. We should also take the vascular system in the heart into account. For example, nitric oxide (NO) is released from endothelial cells. Opioids increase the release of NO from the endothelial cells in the vascular system.[33] Hence, fentanyl could produce increased coronary collateral flow to ischaemic areas during ischaemia, reducing infarction. However, we believe this is unlikely, as no significant differences in coronary flow between groups were detected during ischaemia; moreover, collateral vasculature is not well developed in rat hearts.[34] Interestingly, NO is known to stimulate PKC[35] and K_{ATP} channels.[36] Therefore, fentanyl could have activated PKC and/or K_{ATP} channels via NO to reduce ischaemic damage.

This is the first attempt to determine the effect of an opioid on pure myocardial stunning. Our previous study showed that fentanyl did not alter haemodynamic indices in non-ischaemic hearts.[8] Therefore, the present study suggests that fentanyl did not affect the degree of stunning. Our group has reported previously that postischaemic systolic shortening of the left ventricular wall in fentanyl-anaesthetized rabbits was similar to that in isoflurane-anaesthetized animals.[37] This suggested that fentanyl might be protective against ischaemic injury, for there is general consensus that isoflurane attenuates the degree of ischaemic damage.[1] The reason why fentanyl reduced infarction but not stunning remains to be elucidated. A number of cellular events occur after the onset of ischaemia, and they become progressively more severe with time. The sequence is highly variable and as yet no clear border separating cell survival from death exists.[38] However, one hypothesis might be that there is an essential step in the course of developing ischaemic damage which makes the myocardium destined to die, and that fentanyl delays this process. Meldrum and colleagues suggested that different PKC isoforms are linked to different aspects of myocardial protection against ischaemic injury.[39] Fentanyl might have activated the specific PKC isoforms that reduce infarction but not stunning. Another explanation could be that fentanyl reduced infarction by increasing coronary collateral flow. It was not possible for fentanyl to exhibit protection in our stunning model because this involved global rather than regional ischaemia.

Although TTC staining is a reliable method for the quantification of infarct size,[40] it is not sensitive enough to detect necrosis of a single cell. This implies that a very small amount of infarction might have occurred in our stunning model. However, it is highly unlikely that infarction of a small fraction of myocardium affects the haemodynamics of the whole heart. Thus, we consider our model valid in assessing the degree of stunning.

We conclude that fentanyl limits infarction but does not attenuate stunning, and that this protection against infarction is mediated by an δ-opioid receptors and PKC-linked mechanism in our rat model. Further studies are needed to determine whether the contribution of fentanyl in decreasing infarction could be applied to clinical practice. The elucidation of its mechanism could lead to the development of novel interventions to reduce infarction in the future.

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References

1 Ross S, Foëx P. Protective effects of anaesthetics in reversible and irreversible ischaemia–reperfusion injury. *Br J Anaesth* 1999, **82**: 633–2

2 Schultz JJ, Hsu AK, Gross GJ. Morphine mimics the cardioprotective effect of ischemic preconditioning via a glibenclamide-sensitive mechanism in the rat heart. *Circ Res* 1996, **78**. 1100–4

3 Schultz JJ, Hsu AK, Gross GJ. Ischemic preconditioning and morphine-induced cardioprotection involve the delta (δ)-opioid receptor in the intact rat heart. *J Mol Cell Cardiol* 1997; **29**: 2187–95

4 Miki T, Cohen MV, Downey JM. Opioid receptor contributes to ischemic preconditioning through protein kinase C activation in rabbits. *Mol Cell Biochem* 1998; **186**: 3–12

5 Lawson CS, Downey JM. Preconditioning: state of the art myocardial protection. *Cardiovasc Res* 1993; **27**: 542–50

6 Yellon DM, Baxter GF, Garcia Dorado D, Heusch G, Sumeray MS Ischaemic preconditioning: present position and future directions. *Cardiovasc Res* 1998; **37**: 21–33

7 Meldrum DR, Cleveland JC Jr, Rowland RT, Banerjee A, Harken AH, Meng X. Early and delayed preconditioning: differential mechanisms and additive protection. *Am J Physiol* 1997; **273**: H725–33

8 Kato R, Ross SA, Foex P. Fentanyl protects the heart against ischaemic injury via opioid receptors, adenosine A_1 receptors, and K_{ATP} channels linked mechanism in rats. *Br J Anaesth* 2000, **84**: 204–14

9 Bugge E, Ytrehus K. Bradykinin protects against infarction but does not mediate ischemic preconditioning in the isolated rat heart. *J Mol Cell Cardiol* 1996; **28**: 2333–41

10 Sakamoto J, Miura T, Goto M, Iimura O. Limitation of myocardial infarct size by adenosine A_1 receptor activation is abolished by protein kinase C inhibitors in the rabbit. *Cardiovasc Res* 1995, **29**: 682–8

11 Cleveland JC Jr, Meldrum DR, Rowland RT, Banerjee A, Harken AH. Adenosine preconditioning of human myocardium is dependent upon the ATP-sensitive K^+ channel. *J Mol Cell Cardiol* 1997; **29**· 175–82

12 Bugge E, Ytrehus K. Endothelin-1 can reduce infarct size through protein kinase C and K_{ATP} channels in the isolated rat heart. *Cardiovasc Res* 1996; **32**: 920–9

13 Tsuchida A, Liu Y, Liu GS, Cohen MV, Downey JM. α_1-Adrenergic agonists precondition rabbit ischemic myocardium independent of adenosine by direct activation of protein kinase C. *Circ Res* 1994; **75**. 576–85

14 Maguire P, Tsai N, Kamal J, Cometta Morini C, Upton C, Loew G. Pharmacological profiles of fentanyl analogs at μ, δ and κ opiate receptors. *Eur J Pharmacol* 1992; **213**: 219–25

15 Zimlichman R, Gefel D, Eliahou H, *et al.* Expression of opioid receptors during heart ontogeny in normotensive and hypertensive rats. *Circulation* 1996; **93**: 1020–5

16 Wong TM, Lee AY, Tai KK. Effects of drugs interacting with opioid receptors during normal perfusion or ischemia and reperfusion in the isolated rat heart–an attempt to identify cardiac opioid receptor subtype(s) involved in arrhythmogenesis *J Mol Cell Cardiol* 1990; **22**: 1167–75

17 Wu JP, Chen YT, Lee AY Opioids in myocardial ischaemia potentiating effects of dynorphin on ischaemic arrhythmia, bradycardia and cardiogenic shock following coronary artery occlusion in the rat. *Eur Heart J* 1993; **14**: 1273–7

18 Schultz JJ, Hsu AK, Gross GJ. Ischemic preconditioning in the intact rat heart is mediated by δ_1- but not μ- or κ-opioid receptors. *Circulation* 1998; **97**: 1282–9

19 Schultz JJ, Hsu AK, Nagase H, Gross GJ TAN-67, a δ_1-opioid receptor agonist, reduces infarct size via activation of Gi/o proteins and K_{ATP} channels *Am J Physiol* 1998, **274**: H909–14

20 Tsuchida A, Miura T, Tanno M, Nozawa Y, Kita H, Shimamoto K. Time window for the contribution of the δ-opioid receptor to cardioprotection by ischemic preconditioning in the rat heart. *Cardiovasc Drugs Ther* 1998; **12**: 365–73

21 Liang BT, Gross GJ Direct preconditioning of cardiac myocytes via opioid receptors and KATP channels *Circ Res* 1999; **84** 1396–400

22 Moolman JA, Genade S, Winterbach R, Harper IS, Williams K, Lochner A. Preconditioning with a single short episode of global ischemia in the isolated working rat heart: effect on structure, mechanical function, and energy metabolism for various durations of sustained global ischemia *Cardiovasc Drugs Ther* 1995; **9**: 103–15

23 Simkhovich BZ, Przyklenk K, Kloner RA. Role of protein kinase C as a cellular mediator of ischemic preconditioning a critical review. *Cardiovasc Res* 1998; **40**: 9–22

24 Ventura C, Spurgeon H, Lakatta EG, Guarnieri C, Capogrossi MC. κ and δ opioid receptor stimulation affects cardiac myocyte function and Ca^{2+} release from an intracellular pool in myocytes and neurons. *Circ Res* 1992, **70**: 66–81

25 Sugden PH, Bogoyevitch MA Intracellular signalling through protein kinases in the heart. *Cardiovasc Res* 1995; **30**· 478–92

26 Lou LG, Pei G. Modulation of protein kinase C and cAMP-dependent protein kinase by δ-opioid. *Biochem Biophys Res Commun* 1997; **236**: 626–9

27 Kramer HK, Simon EJ. Role of protein kinase C (PKC) in agonist-induced μ-opioid receptor down-regulation: II. Activation and involvement of the α, ε, and ζ isoforms of PKC *J Neurochem* 1999; **72**: 594–604

28 Brooks G, Hearse DJ. Role of protein kinase C in ischemic preconditioning. player or spectator? *Circ Res* 1996; **79**. 627–30

29 Lasley RD, Noble MA, Mentzer RM Jr Effects of protein kinase C inhibitors in in situ and isolated ischemic rabbit myocardium *J Mol Cell Cardiol* 1997; **29**: 3345–56

30 Lundmark JL, Ramasamy R, Vulleit PR, Schaefer S. Chelerythrine increases Na-K-ATPase activity and limits ischemic injury in isolated rat hearts. *Am J Physiol* 1999; **277**. H999–1006

31 Bugge E, Ytrehus K. Ischaemic preconditioning is protein kinase C dependent but not through stimulation of alpha adrenergic or adenosine receptors in the isolated rat heart. *Cardiovasc Res* 1995; **29**: 401–6

32 Gross GJ, Fryer RM. Sarcolemmal versus mitochondrial ATP-sensitive K^+ channels and myocardial preconditioning. *Circ Res* 1999; **84**· 973–9

33 Stefano GB, Hartman A, Bilfinger TV, Magasine HI, Liu Y, Casares F, *et al.* Presence of the μ_3 opiate receptor in endothelial cells. Coupling to nitric oxide production and vasodilation. *J Biol Chem* 1995; **270**· 30290–3

34 Maxwell MP, Hearse DJ, Yellon DM. Species variation in the coronary collateral circulation during regional myocardial ischaemia: a critical determinant of the rate of evolution and extent of myocardial infarction *Cardiovasc Res* 1987, **21** 737–46

35 Ping P, Takano H, Zhang J, Tang XL, Qiu Y, Li RC, *et al.* Isoform-selective activation of protein kinase C by nitric oxide in

the heart of conscious rabbits: a signaling mechanism for both nitric oxide-induced and ischemia-induced preconditioning. *Circ Res* 1999; **84**: 587–604

36 Shinbo A, Iijima T. Potentiation by nitric oxide of the ATP-sensitive K^+ current induced by K^+ channel openers in guinea-pig ventricular cells. *Br J Pharmacol* 1997; **120**: 1568–74

37 Piriou V, Ross S, Pigott D, Evans R, Foex P. Beneficial effect of concomitant administration of isoflurane and nicorandil. *Br J Anaesth* 1997; **79**: 68–77

38 Hearse DJ. Myocardial protection during ischemia and reperfusion. *Mol Cell Biochem* 1998; **186**: 177–84

39 Meldrum DR, Cleveland JC Jr, Meng X, Sheridan BC, Cain BS, Harken AH, *et al.* Protein kinase C isoform diversity in preconditioning. *J Surg Res* 1997; **69**: 183–7

40 Ito WD, Schaarschmidt S, Klask R, Hansen S, Scafer HJ, Mathey D, *et al.* Infarct size measurement by triphenyltetrazolium chloride staining versus in vivo injection of propidium iodide. *J Mol Cell Cardiol* 1997; **29**: 2169–75

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REVIEW ARTICLE

Thermoregulation, mild perioperative hypothermia and post-anaesthetic shivering

D. J. Buggy[1]* **and A. W. A. Crossley**[2]

[1]*University Department of Anaesthesia, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK*
[2]*Department of Anaesthesia, Southern Derbyshire Acute Hospitals Trust, Derby, UK*
**Corresponding author: e-mail:dbuggy@talk21.com*

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Keywords: complications, hypothermia; complications, shivering

The maintenance of normothermia is an important function of the autonomic nervous system in homeothermic mammals such as man, as cellular and tissue dysfunction become evident at even minor deviations from normal core body temperature.[48 53 113] In man, core temperature is normally maintained within narrow limits of 36.5–37.5°C,[48] even in the presence of an adverse environmental temperature, by a combination of behavioural and physiological responses. Anaesthesia abolishes behavioural mechanisms and has the potential to disrupt the physiological mechanisms of thermoregulation. Adverse postoperative outcomes, including wound infection, increased surgical bleeding and morbid cardiac events are being associated with mild perioperative hypothermia (33.0–36.4°C).[21 22 26 42–44 52 74 80 84 85 90 109] There is in turn, increased interest in its prevention and treatment, using physical and pharmacological therapy. Hyperthermia or fever, rather than hypothermia, is a more common problem in critically ill patients in intensive care units and has been the subject of a recent editorial.[19] In this review, we concentrate on the mild, inadvertent hypothermia which frequently accompanies clinical anaesthesia.

The strict physiological definition of hypothermia is core temperature greater than one standard deviation (SD) below the mean core temperature for that mammal, under resting conditions in a thermoneutral environment.[10] Studies on healthy human volunteers have shown that normal human core temperature can range from 36.5 to 37.5°C, with mean values consistently 36.9–37.0 (0.2–0.5)°C.[75 79 82 98] Core hypothermia may thus be said to commence at 36.4°C, but the lower threshold at which mild hypothermia becomes moderate hypothermia is less clearly defined. We have taken the clinical anaesthetist's working definition of mild hypothermia as 33.0–36.4°C, the approximate temperature at which organ dysfunction may begin to develop.[53 113]

Physiology

Thermoregulation is achieved by a physiological control system consisting of peripheral and central thermoreceptors, an integrating control centre and efferent response systems which take compensatory action.[113] Afferent thermal input comes from anatomically distinct cold and warmth receptors, which may be peripheral or central.[53] The central control mechanism, situated in the hypothalamus, determines mean body temperature by integrating thermal signals from peripheral and core structures, and comparing mean body temperature with a pre-determined 'set-point' temperature.[48] In man, the efferent response to effect change in body heat content as required is by behavioural and autonomic means. The latter involves control of cutaneous vascular smooth muscle tone, shivering and non-shivering thermogenesis when increased heat production is indicated, and sweating when heat loss is indicated.[86] Behavioural responses are of importance in both warm and cold challenges, particularly the latter, where in man they are quantitatively more important than the autonomic mechanisms (Fig. 1).

Afferent thermal signals

Much of our knowledge of the structures of the thermoregulatory system has been gleaned from animal studies. The afferent thermal input may be central or peripheral. Thermally sensitive receptors located in the skin and mucous membranes mediate thermal sensation and contribute to thermoregulatory reflexes. Most of these receptors are not necessarily thermospecific and may also mediate mechanical sensation.[48 100] Cold-specific receptors have a peak rate of discharge of impulses at 25–30°C.[48 53] They are innervated by type A-δ nerve fibres. Warm receptors, on the other hand, have maximal discharge rate at 45–50°C and are innervated by type C nerve fibres.[100]

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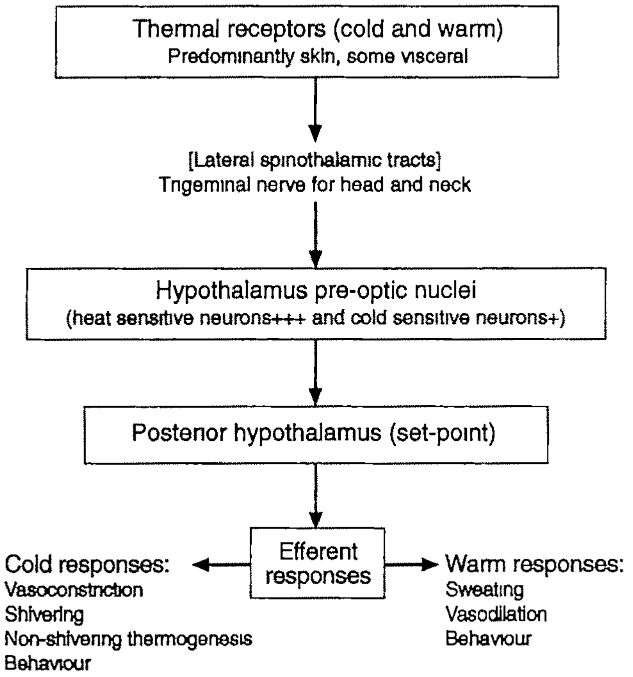
Thermal receptors (cold and warm)
Predominantly skin, some visceral
[Lateral spinothalamic tracts]
Trigeminal nerve for head and neck
Hypothalamus pre-optic nuclei
(heat sensitive neurons+++ and cold sensitive neurons+)
Posterior hypothalamus (set-point)
Cold responses:
Vasoconstriction
Shivering
Non-shivering thermogenesis
Behaviour
Efferent responses
Warm responses:
Sweating
Vasodilation
Behaviour

Fig 1 Control of thermoregulation

Cold receptors respond both to long-term, gradual decreases and to sudden, transient changes in environmental temperature. Transient, violent responses to rates of change in environmental temperature are followed by lasting responses to chronic low levels of skin temperature. This finding was confirmed by Benzinger in a series of experiments in humans subjected to cold water bath stimulation.[7] He studied chemical thermoregulation, which refers to changes in metabolic heat production, usually measured by oxygen consumption. In response to sudden skin temperature reduction by immersion in cold water, oxygen consumption increased acutely and remained elevated, even after the cold stimulus was removed, in response to repeated cold exposure. These findings, together with the observation of 'overshoot inhibition' of oxygen consumption in response to skin surface warming, led to the conclusion that chemical thermoregulation of cold is excited by skin cold receptors and is inhibited by central warm reception.[7 39] Cold receptors in the skin are the major way the body protects itself against cold temperatures, and afferent input from these cold receptors in the skin transmitted to the hypothalamus.[7 8 48]

In addition to peripheral cold receptors, there are central cold receptors of uncertain anatomical location. Their effects are masked by the predominant peripheral influence. Metabolic heat production at warm skin temperatures increases when the core is cooled to less than 36°C.[39] Moreover, it has been demonstrated that some hypothalamic neurones increase their rate of discharge with decreasing core temperature,[51] which is consistent with the observation that there may be impaired response to cold after preoptic hypothalamic lesions[131] or injection of central nervous system (CNS) depressant drugs into the anterior hypothalamus.[130] Central cold thermoreception is considerably less important than peripheral cold sensory input, but studies in patients with spinal cord transection have suggested that this central thermoregulatory process becomes active when the core temperature approaches the lower limit of its set-point range and is less sensitive than the peripheral thermoreceptors.[38]

Central integration – the hypothalamus

Much of the knowledge about the temperature-regulating structures of the hypothalamus has been derived from animal models. The afferent thermal information mechanisms described feed back to temperature-regulating centres in the hypothalamus (Fig. 1). The anterior hypothalamus conducts the integration of afferent thermal information, whereas the posterior hypothalamus controls the descending pathways to effectors.[53] Experiments in animals using thermode technology, whereby a needle-like structure may be placed in minute areas of the brain and its temperature varied by changing the temperature of water passing concentrically within it, have been influential in determining the role of specific brain areas.[13 39 67] The pre-optic area of the hypothalamus contains temperature-sensitive and temperature-insensitive neurones. The former may be subdivided into heat-sensitive and cold-sensitive neurones. The heat-sensitive neurones, which predominate by four to one,[11] increase their discharge rate in response to increased local heat and this activates heat loss mechanisms. Cold-sensitive neurones, conversely, increase their rate of discharge in response to cooling of the pre-optic area of the hypothalamus.[12 14] Neurones sensitive to local thermal stimuli also exist in the posterior hypothalamus, reticular formation and medulla, and spinal cord.[36 65 97]

The posterior hypothalamus integrates cold afferent signals from the periphery with heat-sensitive stimulation from the pre-optic area of the hypothalamus and instigates effector responses. Detection of cold differs from detection of heat, in that it relies on afferent impulses from cutaneous cold receptors,[7 104] rather than reduced discharge rates of the heat-sensitive neurones in the preoptic area.[68] By the time the core body temperature has fallen 0.5°C below normal, the preoptic neurones have become completely inactive so that their signal level cannot be decreased any further. Rather, detection of cold relies on cutaneous cold receptors.[7 104] Although the skin contains both cold and warm receptors, there are 10 times as many cold receptors as warm receptors.[53 104]

Human studies have confirmed that autonomic thermoregulation is dominated by four neural mechanisms: central detection of warmth; peripheral detection of cold; central warm-inhibition of the metabolic response to cold; and finally, inhibition of thermoregulatory sweating by cooling of the skin. The last of these is an antihomeostatic mechanism, which serves to prevent soaking of the skin during strenuous exercise in cool environments.[7 8] In

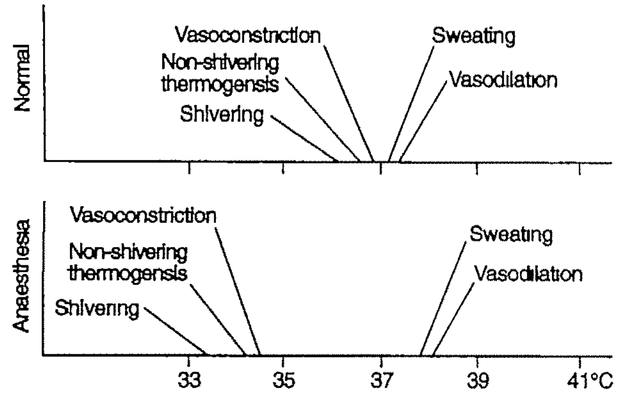

Fig 2 Activation of thermoregulatory effector responses is triggered at specific temperatures for a given individual ('threshold temperature') Note that under general anaesthesia, the threshold temperatures for activation of cold effector responses (including vasoconstriction and shivering) are 'decreased', whereas those for activation of warm responses (including sweating and vasodilation) are 'increased'. Thus, the narrow range of temperature between the vasoconstriction and sweating thresholds (normally ~0.4°C) is widened during general anaesthesia to ~4.0°C. These data are derived from healthy, fasting human volunteers, with ambient temperature ~23°C and relative humidity 40%. Reproduced, with permission, from Ref 113.

humans, the 'set-point' temperature may be defined as the narrow temperature range (typically 36.7–37.1°C) across which there is no effector response.[7] [113] The set-point has variously been termed a 'thermoneutral zone' or 'inter-threshold range', and is unique to humans. Most mammals are better insulated (usually by fur) than man and use variation in heat production to achieve thermal balance.[53] The limits of this narrow range of temperature are the thresholds at which cold or warm responses are instigated. It is normally no more than 0.4°C, but may be increased to as much as 4.0°C during general anaesthesia in human volunteers (Fig. 2).[113–117] Human studies have also demonstrated a diurnal variation of the set-point, varying from approximately 36.2°C during sleep and in the early morning, to as much as 1°C higher in the evening (6–11 pm). Females have a higher set-point temperature during the luteal phase of the menstrual cycle by ~1°C.[50] [53] Rabbit studies have shown that pyrogens may alter the set-point, increasing its triggering temperature by suppressing the activity of warm-responsive neurones, an effect which is reversed by aspirin.[18] Intracranial pathology, such as a space-occupying lesion and dehydration, may also cause an increase in set-point temperature by an unknown mechanism acting upon the temperature-sensitive hypothalamic neurones.[76] The effect of anaesthesia and drugs on thermoregulation and its effector mechanisms is discussed later.

Effector responses.

The thermoregulatory responses are characterized by: (i) altered behaviour, quantitatively the most effective mechanism; (ii) a vasomotor response, consisting of vasoconstriction and piloerection in response to cold, and vasodilation and sweating in response to heat; and (iii) shivering and increased metabolic rate.

In the conscious individual, behaviour modification is more powerful than the autonomic mechanisms of regulating body temperature. When the hypothalamic thermostat indicates an excessively cool body temperature, impulses pass from the hypothalamus to the cerebral cortex to give the individual the sensation of feeling cold. The result is modified behaviour, such as increased motor activity, moving to warmer surroundings or adding additional clothing. The control of behavioural responses to cold is based largely on cutaneous thermal signals (see above).[142]

While the precision of the autonomic control of thermoregulation is very high, the power of these mechanisms is limited to less than the equivalent of four basal metabolic rates on either side of the tightly-controlled set-point.[8] Once the set-point temperature range, typically 36.7–37.1°C, has been breached, autonomic effector responses are activated. Each of the specific responses has a characteristic threshold (activation at a specific temperature), gain (rate of response increase as deviation from normal increases) and maximum response intensity.

Benzinger demonstrated that the response to a central cold challenge (e.g. by asking volunteers to consume 500 g ice in a cool environment, 12°C) consisted of a dramatic increase in metabolic rate, which was detected by an increase in oxygen consumption. Moreover, when a subject with a low core temperature (36.1°C) was passively lowered into a 28°C bath, in order to provide a skin cold challenge, metabolic rate also increased ~ 3-fold.[7] In order to understand the interaction of central warm reception and peripheral cold reception, large, independent variations of skin temperatures from 12 to 38°C and tympanic core temperatures from 36 to 38°C were studied in terms of oxygen consumption and sweating rates. The subjects were healthy, naked young men. The values were then plotted on a graph of core temperature versus oxygen consumption (Figs 3 and 4). At first, there seemed no logical interpretation, but when skin isotherms were drawn, graphing core temperature versus oxygen consumption at a given skin temperature, the thermoregulatory response to cold was clarified. In Fig. 3, as the core temperature increases from cold levels (36.6°C) towards the set-point (in this subject, 37.1°C), oxygen consumption and metabolic endogenous heat production decrease at all skin temperatures, but at cold skin temperatures (e.g. 20°C), metabolic heat production continues until the core temperature is warmer than would have been the case if the skin temperature had been 30°C. Once the set-point core temperature is reached, basal metabolic heat production applies, assuming the subject remains at rest. The right-hand portion of Fig. 3 also indicates that as the core temperature increases above the set-point, heat loss mechanisms are strongly activated, as seen in the increased rate of heat loss from evaporation of sweat.[7] Conversely, the effect of increasing skin temperature

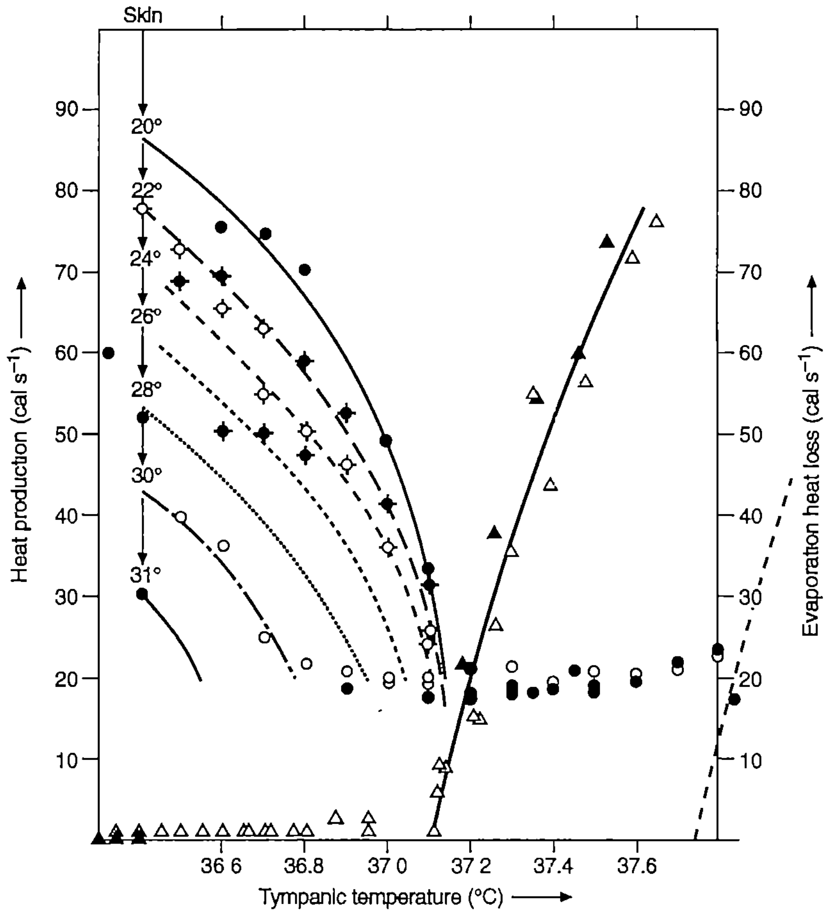

Fig 3 Effect of core temperature on metabolic heat production at different skin temperature isotherms Note that when skin temperature is relatively cold (20°C), metabolic heat production remains high until the core temperature is >37°C. Data derived from healthy human volunteers Reproduced, with permission, from Ref. 7.

on metabolic heat production at different core temperature isotherms is shown in Fig. 4.

Shivering and non-shivering thermogenesis

A motor centre for shivering exists adjacent to the centre in the posterior hypothalamus on which the impulses from cold receptors impinge. It is normally inhibited by impulses from the preoptic heat-sensitive area in the anterior hypothalamus, but when the cold impulses exceed the rate at which the former may be received, this motor centre for shivering becomes activated by 'spill-over' of signals and sends impulses bilaterally into the anterior motor neurones of the spinal cord. Initially, this increases the tone of skeletal muscles throughout the body, but when this muscle tone rises above a certain level shivering is observed. This is achieved by increasing the sensitivity of the skeletal muscle stretch reflex.[48 50 53] Two patterns of muscular activity, seen in electromyography studies, contribute to the phenomenon of post-anaesthetic shivering in humans, and are discussed below.[129] While post-anaesthetic shivering may aggravate hypoxaemia,[4] recent work in a rabbit model has suggested that mild hypoxaemia may actually inhibit shivering, by reducing the shivering threshold by more than 1°C.[66]

The elicitation of non-shivering thermogenesis by thermoregulatory noradrenaline release is an important effector mechanism in increasing heat production particularly in neonates.[32] These hormonal mechanisms are particularly important in long-term adaptation to cold. Non-shivering thermogenesis occurs mainly in brown adipose tissue (BAT). This subtype of adipose tissue contains large numbers of mitochondria in its cells and these are supplied by a strong sympathetic nervous system (SNS) innervation. When sympathetic stimulation occurs, oxidative metabolism of the mitochondria is stimulated but is uncoupled to phosphorylation, so that heat is produced instead of generating the metabolic fuel, adenosine triphosphate (ATP). In human adults, the amount of BAT is small and non-shivering thermogenesis increases the rate of heat production by less than 10–15%, in contrast to infants, where it can double heat production.[32] The sympathetic response to mild intraoperative hypothermia and non-shivering thermogenesis are abolished by fentanyl-propofol anaesthesia in infants.[101] An audit of post-anaesthetic shivering in a dedicated paediatric hospital found an overall incidence of shivering of 14% with older age (>6 yr), administration of atropine and intraoperative hypothermia being significantly predictive of shivering.[88]

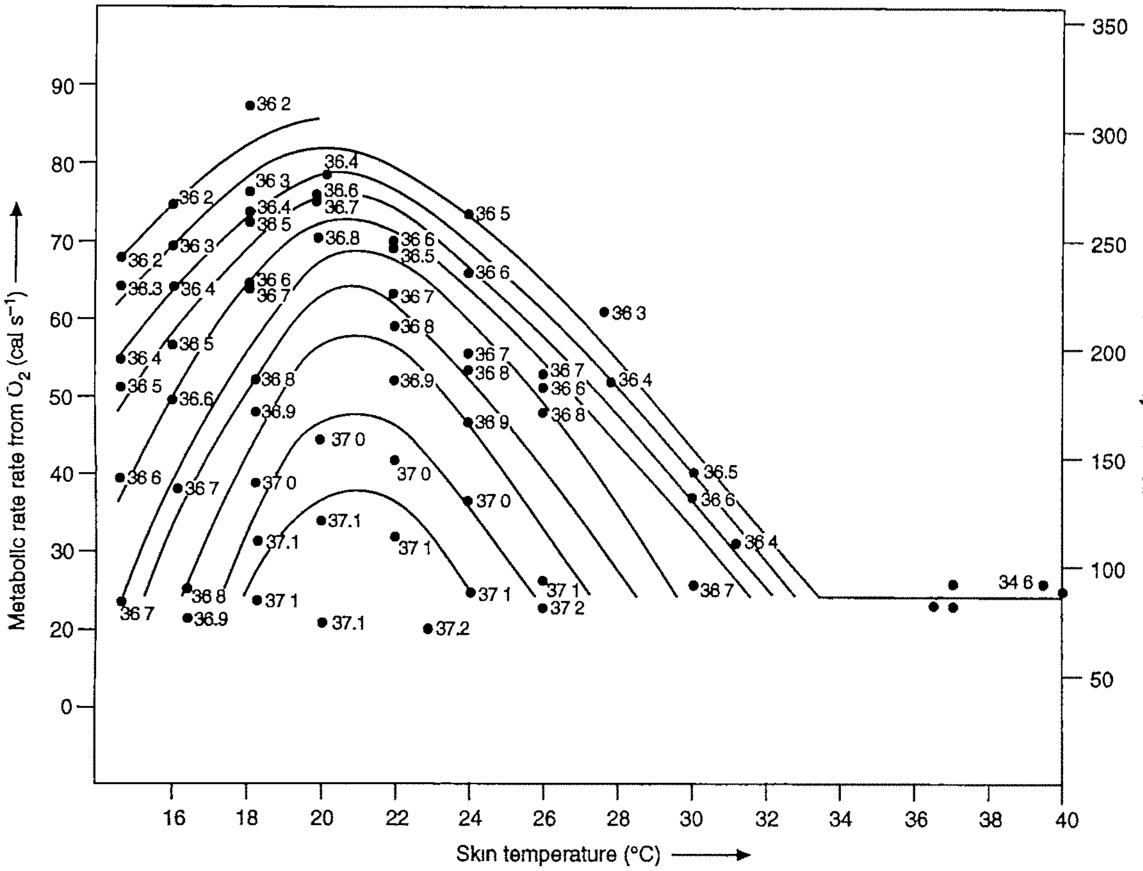

Fig 4 Effect of skin temperature on metabolic heat production at different core temperature isotherms. Note that when the core temperature is relatively cold (36.3°C), metabolic heat production remains high until the skin temperature is >32°C Data derived from healthy human volunteers Reproduced, with permission, from Ref 7.

Heat balance

Heat is a form of energy and temperature is a measure of the amount of heat in a body. Heat balance refers to the total amount of heat in the body, and is increased by metabolic heat production and reduced by evaporation of sweat. Radiation, conduction and convection may increase or decrease the body heat content, depending on environmental circumstances. For example, if ambient temperature is greater than body temperature, radiation will increase body heat content, while the reverse will occur when ambient temperature is less than body temperature.[48] Heat gain processes may be *obligatory*, that is they occur without reference to thermoregulation; or *facultative*, that is they can be manipulated by thermoregulatory mechanisms to restore heat balance. Obligatory heat gain necessarily includes basal metabolic rate (BMR). This is the energy cost of maintaining normal homeostasis within the body and is approximately 40 kcal m^{-2} h^{-1}.[53] It is increased in childhood, in the presence of sympathetic nervous system stimulation by fever, and by hormones such as thyroxine, androgen and growth hormone. It declines with age and is reduced during sleep and malnutrition. Facultative heat gain includes: physical exercise, which if strenuous can increase heat production to 20 times BMR; shivering, which can increase it sixfold above BMR;[53] and non-shivering thermogenesis, which is particularly important in the neonate, but not in adults.[32] Digestion of foods, especially proteins, also has a thermogenic effect.[110–112]

Heat loss at rest is predominantly (75%) by conduction, convection and radiation, with convection being the most important. Convective heat loss occurs when the layer of air next to the skin moves or is disturbed, thereby removing its insulative properties. Radiative heat loss is proportional to the fourth power of the temperature difference between the patient and the ambient environment.[113] The remaining 25% of heat loss at rest is evaporation of insensible water, principally evaporation from the respiratory tract. Sweating involves the active secretion of water on the skin, and because the specific latent heat of vaporization of water is 0.58 Cal g^{-1}, its evaporation can dissipate large amounts of heat, up to 20 times BMR.[48]

Inadvertent hypothermia is by far the most common perioperative thermal abnormality seen, and it results from exposure to a cold environment in a context of impaired thermoregulatory mechanisms.[23] Patients whose normal core temperature is 37°C are anaesthetized and their skin exposed in an operating theatre with an ambient temperature of 20–25°C. The cooling that results is aggravated by the use of cold antiseptic solutions which are allowed to evaporate from the skin, or by cool fluids instilled into body cavities and by cool intravenous infusions which increase conductive losses. Air turnover rates in theatre (typically 20 cm s^{-1}) will influence convective heat loss.[113]

Measurement of body heat content cannot be achieved directly. However, it may be derived from the product of mean body temperature, body mass and the specific heat of the body. An estimate of mean body temperature (T_{body}) may be obtained from this equation, derived from calorimetric studies:

$$T_{body} = 0.66\ T_{core} + 0.34\ T_{skin},$$

where T_{core} = core body temperature and T_{skin} = mean skin temperature.[28] The accuracy of this equation relies in turn on the adequacy of mean skin temperature measurement. Different areas of skin may be given a different weighting depending on the amount of body surface area it represents.[40] When a high degree of accuracy is required, the mean skin temperature may be estimated using 10 or more skin measurement sites.[123] However, Ramanathan suggested that four skin measurement sites provide adequate accuracy in this calculation without the inconvenience of using a larger number of sites, and this approach has been used successfully in a clinical setting.[55 107] It has been shown that the choice of site for core temperature measurement and the weighting coefficients used in calculating mean body temperature are more important sources of error than is the calculation of mean skin temperature.[106]

Core temperature can reliably be evaluated at the tympanic membrane, distal oesophagus and pulmonary artery. Intraoperative thermal monitoring may be achieved with infrared thermometry of the tympanum or by thermistors placed in the distal oesophagus. Core temperature may also be estimated with nasopharyngeal, axillary, rectal and bladder temperatures, although rectal temperature lags behind other core sites.[29] Skin surface temperature varies with ambient temperature and with induction of anaesthesia, and is usually also measured with a thermistor, or alternatively with a liquid crystal thermometer.[93 113] Measurement of temperature at the skin surface has been used to estimate the core temperature, by heating the sensor to eliminate the core–surface temperature gradient. Deep tissue temperature monitoring in this way at the sternum and forehead correlate well with distal oesophageal temperature (r^2 = 0.7, mean difference from oesophageal temperature = 0.2°C).[93]

Hypothermia during general anaesthesia follows a distinctive pattern and occurs in three phases: an initial rapid decrease in core temperature of ~1°C over the first hour, followed by a slower linear decrease to 34–35°C, after which point a core temperature plateau or thermal equilibrium is reached, where heat loss to the periphery equals heat gained from core metabolic production.[113] The initial rapid reduction in core temperature is greater than that which would be explained by a lowering of metabolic rate and heat loss, and is in fact attributable to core-to-peripheral redistribution of body heat.[54 94] Mean body temperature and body heat content remain constant during this first hour.[116 119] The subsequent core temperature plateau is largely due to thermoregulatory vasoconstriction, triggered by a core temperature of 33–35°C.[5 117]

Effect of general anaesthesia on thermoregulation

Behavioural thermoregulation is redundant during general anaesthesia, and both general and regional anaesthesia obtund normal temperature control mechanisms. The anaesthetist must thus manage the patient's thermoregulatory control. General anaesthesia causes thermoregulatory impairment characterized by an increase in warm-response thresholds and a decrease in cold-response thresholds, such that the normal interthreshold range (between which no effector response occurs) is increased from ~0.4°C to 4.0°C.[115] Both warm-response and cold-response thresholds are affected (Fig. 2). These values have been derived from human volunteer studies, using tympanic thermometry, with ambient temperature usually around 25°C.

All general anaesthetic agents impair thermoregulatory responses to a similar, but not identical, extent. All the currently used potent inhalation anaesthetic agents decrease the vasoconstriction and shivering thresholds (Table 1).[41 62 75 78 98 116] Isoflurane produces a dose-dependent decrease in the threshold for thermoregulatory vasoconstriction, ~3°C per 1% isoflurane concentration.[132] Isoflurane also reduces the shivering threshold and changes the pattern of shivering to include a more clonic type of muscular activity. The latter involves a change from a linear increase in shivering intensity to bouts of intense, clonic shivering followed by quiescent periods.[62] In addition, isoflurane reduces maximum shivering intensity,[62] but gain is generally preserved during general anaesthesia.[132] Desflurane, however, decreases both the threshold and gain of vasoconstriction, the latter threefold from 2.4 to 0.8 ml min^{-1} per °C.[82] Sevoflurane has been shown to produce a dose-dependent reduction in shivering threshold in rabbits.[49] Similarly, the thresholds of the warm-responses, sweating and vasodilatation are increased by inhalation anaesthesia.[138] Thus the effects of anaesthesia on thermoregulatory responses differ from its effects on the carbon dioxide response curve, which displays both increased threshold and decreased gain.[113] During general anaesthesia the thermoregulatory thresholds are lowered further in elderly patients (60–80 yr) than in younger patients, by as much 1°C.[79]

Recently, a study comparing induction of anaesthesia with either sevoflurane or propofol found greater core hypothermia in patients receiving propofol, even though they were subsequently ventilated on sevoflurane and nitrous oxide. These data suggest that even a brief period

Table 1 Characteristics of the cold effector responses in controls and during anaesthesia. All of these studies were on human subjects. N/A indicates data not clearly available. [a]Gain was calculated from laser Doppler fluorimetry; other data on thermoregulatory gain was calculated from oxygen consumption

	Threshold (°C)	Gain (ml O_2 min^{-1} °C^{-1})	Max response intensity (ml O_2 min^{-1} °C^{-1})
Normal vasoconstriction	36.8±0.4[78] 36.6±0.2[41]	2.4[a] [82]	N/A
Vasoconstriction under GA	35.6±0.3[78] 34.6±0.4[116]	0.8[a] [82]	N/A
Vasoconstriction with epidural	36.2±0.4[41] 36.5±0.2[98]	N/A	N/A
Control shivering	35.7±0.4[98] 36.7±0.6[75]	−580±186[75]	607±82[75] 706±144[62]
Shivering with GA	34.2±0.8[64]	−1480±750[62]	490±80[62]
Vasoconstriction with spinal	36.7±0.3[98]	N/A	N/A
Shivering with spinal	35.5±0.5[98]	N/A	N/A
Shivering with epidural	35.4±0.5[98] 36.3±0.5[75]	−215±154[75]	412±50[75]

of propofol-induced vasodilation causes significant redistribution hypothermia.[63] Intramuscular midazolam 0.075 mg kg^{-1} produced a dose-dependent reduction in tonic thermoregulatory vasoconstriction, significantly reducing core temperatures, even in the absence of conventional anaesthesia.[91]

The effect of general and regional anaesthesia on effector responses is summarized in Table 1.

Effect of regional anaesthesia on thermoregulation

Epidural and spinal anaesthesia decrease the vasoconstriction and shivering thresholds to a comparable degree,[98] but by a lesser amount, of ~0.6°C, than general anaesthetics when measured above the upper level of the block.[81 98 118] Because local anaesthetics administered to the central neuraxis do not directly interact with the hypothalamic control centres and local anaesthetics given intravenously in doses equivalent to plasma levels after epidural anaesthesia have no thermoregulatory effect,[47] the mechanism of this disturbance during regional anaesthesia is unknown, but is consistent with thermoregulatory impairment caused by the effects of the regional block upon afferent thermal information.[81]

In contrast to general anaesthesia, where the gain of thermoregulatory responses is unchanged, the gain of shivering is reduced by 63% and the maximum intensity by 33% following epidural anaesthesia (Table 1). This occurs because shivering above the block compensates for the inability of muscles below the block to engage in shivering.[75] As with general anaesthesia, core hypothermia (by 0.6–1.5°C) occurs during the first hour or so after epidural anaesthesia, due to core-to-peripheral redistribution of body heat from the epidural-induced vasodilation. However, with prolonged epidural anaesthesia, the degree of core hypothermia was less than after general anaesthesia, because of vasoconstriction above the level of the block.[92]

Shivering during regional anaesthesia is, like that after general anaesthesia, preceded by core hypothermia and vasoconstriction above the level of the block, and in addition, has the same electromyography characteristics as that which occurs after general anaesthesia.[61] With reduced gain and maximum intensity, the shivering which is induced by core hypothermia after regional anaesthesia is usually ineffective in preventing core hypothermia, although it has been reported that after treatment of shivering the core temperature may fall further.[122]

Whether shivering seen during epidural analgesia in labour is due to the temperature of the injectate is unclear. Injection of ice-cold epidural local anaesthetic increases shivering compared with epidural solutions that are prewarmed to 30°C.[102] This result was not repeated in non-pregnant patients, however, where no difference in the incidence of shivering was observed between those given warm or cold epidural injections.[103] Shivering during a regional anaesthetic may be averted by maintaining high ambient temperature,[103] by skin-surface warming with radiant heat,[124] or by using the same drugs that are effective for shivering after general anaesthesia (see below).

Interestingly, core hypothermia during regional anaesthesia may not trigger a sensation of cold.[41] This may reflect the fact that subjective cold perception depends on skin temperature afferent input, and that the cutaneous vasodilatation resulting from regional anaesthesia increases skin temperature, leading to a sensation of warmth although accompanied by thermoregulatory shivering.[118] Awareness of core hypothermia is also impaired by epidural anaesthesia.[41]

After the core-to-peripheral redistribution of body heat with induction of general and regional anaesthesia, subsequent further hypothermia depends on the balance of cutaneous heat loss and rate of heat metabolic heat production.[113] During regional epidural anaesthesia, there are two factors which may accelerate heat loss and prevent the emergence of a core temperature plateau seen after general anaesthesia: firstly, there is reduced vasoconstriction threshold in conjunction with lower limb vasodilation due to the block itself. Hence heat loss continues unabated during epidural anaesthesia despite the activation of the effector mechanisms above the level of the block. This is especially seen where general and epidural anaesthesia are combined.[73]

Secondly, epidural anaesthesia further reduces the vasoconstriction threshold during general anaesthesia and increases the rate of core cooling compared with general anaesthesia alone, because vasoconstriction in the quantitatively important leg compartment is inhibited by the block.[73]

Consequences of mild perioperative hypothermia

In particular circumstances, hypothermia may have a protective effect in terms of reducing basal metabolic rate and with it the risk of tissue hypoxia and ischaemia. The efficacy of mild hypothermia in reducing the cerebral metabolic requirement for oxygen exceeds that of barbiturate coma[133 134] and hence may be indicated in carotid arterial surgery or neurosurgery. Moderate hypothermia is routine practice in many cardiac surgery centres using cardiopulmonary bypass, to minimize the risk of myocardial and cerebral ischaemia. It is generally agreed however that the deleterious consequences of mild hypothermia outweigh the potential benefits,[23] with evidence emerging that hypothermia *per se* is responsible for adverse postoperative outcomes. Hypothermia is associated with shivering and excessive sympathetic nervous system stimulation;[43] metabolic acidosis causing prolonged drug metabolism, particularly of neuromuscular antagonists and propofol;[52 85 95] and delayed recovery from anaesthesia.[84] Platelet activity is impaired,[135] and there is prolongation of the coagulation time and decreased clot formation rate.[37 70] Impaired immune function and delayed wound healing have been demonstrated,[127 136] and hypothermia is associated with both increased breakdown and decreased synthesis of muscle protein.[21 22 24] Perioperative thermal discomfort is often remembered by patients as the worst aspect of their perioperative experience.[120]

The hypothesis that perioperative normothermia increases susceptibility to surgical wound infection and lengthens hospitalization was tested in a prospective, randomized trial.[80] Two hundred patients undergoing colorectal surgery were randomly assigned to a routine intraoperative thermal care group (hypothermia group) and an additional warming group (normothermia group). Wounds were evaluated daily until discharge and they were deemed infected if culture-positive pus was isolated. Nineteen percent (19%) of the hypothermia group compared with 6% of the normothermia patients developed wound infections ($P<0.001$). The duration of the hospital stay was also prolonged in the hypothermia group to 13.5±4.5 *vs* 11.8±4.1 days ($P=0.01$). In the hypothermic group, hypothermia persisted for 4 h postoperatively, and their end-of-surgery core temperatures were 34.7°C compared with 36.6°C in those actively warmed. The initial 3–4 h after bacterial contamination are thought to be crucial in determining whether clinical infection ensues.[27]

In vitro studies suggest that platelet and coagulation function are impaired by hypothermia.[37 70 136] The hypothesis that hypothermia may affect surgical bleeding and allogeneic transfusion requirements was also tested in a prospective, randomized trial.[109] Sixty patients undergoing total hip arthroplasty were randomized to normothermia (final core temperature 36.6°C) or mild hypothermia (35.0°C), as described above.[80] Hypothermic patients lost 2.2(0.5) compared with 1.7(0.3) litres of blood (mean(SD), $P<0.001$). Significantly more blood transfusions were required in the hypothermic group.

A number of studies have suggested that mild hypothermia increases cardiac ischaemia and perioperative mortality. A retrospective study showed that the incidence of myocardial ischaemia postoperatively in a group of patients undergoing vascular surgery was raised from 13% to 36% if the patients had a sublingual temperature less than 35°C at the end of the procedure.[42] A prospective, randomized controlled trial comparing over 300 patients with coronary artery disease who either had routine care (and hence were allowed to develop mild hypothermia) or were actively maintained at normothermia during major, non-cardiac surgery found that maintenance of normothermia was associated with a reduced incidence of angina, myocardial infarction, ventricular tachycardia and cardiac arrest than the mildly hypothermic group.[44]

The thermoregulatory response thresholds are lowered during general anaesthesia by 1°C more in elderly patients (60–80 yr) than in younger patients,[79] making them more vulnerable to the occurrence of hypothermia. Prevention of hypothermia in this age group reduces negative nitrogen balance associated with increased protein breakdown or decreased protein synthesis.[21 22]

Physical, active and passive strategies for avoiding perioperative hypothermia

Preventing redistribution-induced hypothermia may be achieved by skin-surface warming. Redistribution of heat occurs when anaesthetic-induced vasodilatation allows heat to flow from the core to the shell down its concentration gradient, effectively abolishing the shell. Pre-emptive skin surface warming, for example by using a forced air-warming device, does not increase core temperature but increases body heat content, particularly in the legs, and removes the gradient for heat loss via the skin.[58] This approach is rarely used in clinical practice, however, because it requires 1 h of prewarming. A shorter, more aggressive period of warming may result in counterproductive sweating and discomfort.[121]

Passive insulation, including cotton drapes, has been used perioperatively to reduce heat loss to the environment,[116] the surface area covered with passive insulation being the important determinant of its effectiveness.[117] However, warming these passive insulators or adding more layers does not improve heat conservation significantly, and passive warming systems are not likely to be effective in longer, more extensive operations.[120] However, a comparison of two passive warming systems during major hepatopancreatic surgery, one with heat reflective properties, unexpectedly found that both core and skin temperature increased in 40%

of patients in each group. This phenomenon may have been due to endogenous heat stimulation by this particular form of surgery.[33] A further study, comparing the efficacy of passive with active skin surface warming, was undertaken in patients undergoing hip arthroplasty. The forced air-warming system was most effective at maintaining normothermia, in comparison with aluminized foil. The latter reduced skin heat loss only, but was unable to prevent the core hypothermia that resulted from core-to-peripheral heat redistribution.[6] Nonetheless, aluminized metallic foil has been shown to increase skin temperature and decrease post-anaesthetic shivering, even after relatively short general anaesthetics,[17] but not during epidural analgesia for labour.[15]

Because only 10% of metabolic heat production is lost in heating and humidifying inspired gases, this method is relatively ineffective at maintaining normothermia.[59] Heat- and moisture-exchanging filters retain significant amounts of moisture and heat within the respiratory system, but are only half as effective as active mechanisms (and only half as expensive).[9] Ambient temperature determines the rate of heat loss by radiation and convection, and should be >23°C to optimally contribute to maintaining normothermia. However, operating room staff usually find these temperatures uncomfortable. Water mattresses are demonstrably ineffective at preventing heat loss, possibly because relatively little heat is lost from the back.[96] Moreover, decreased local tissue perfusion associated with local temperatures of 40°C may lead to skin necrosis.[96] Conductive losses may be reduced if intravenous fluids are warmed before or during administration.[128]

Forced air-warming systems are undoubtedly the best way to maintain normothermia during long procedures, and are particularly effective when used intraoperatively on vasodilated patients, thereby allowing the heat applied to be rapidly transferred to the core. They increase core temperature both intraoperatively and postoperatively, reducing the incidence of post-anaesthetic shivering and thermal discomfort.[6 45 77]

A novel approach to maintaining perioperative normothermia has recently been proposed, based on the principle of prevention. An intravenous infusion of an amino acid mixture commenced before and continued during anaesthesia was found to stimulate metabolic heat production five-fold, compared with the thermogenic effect of amino acids observed in the unanaesthetized state. This thermogenesis was associated with an increased body temperature[110] which originated predominantly from the extra-splanchnic circulation.[112] However, the increased temperature was achieved not only by increased non-shivering thermogenesis, but also by vasoconstriction, reducing cutaneous heat loss.[110 111] The mechanism for this enhanced thermogenic potential during general anaesthesia is as yet unclear. One hypothesis is that in the unanaesthetized subject, there is central inhibition of oxidative metabolism in response to nutrients when the core temperature exceeds the set-point temperature. General anaesthesia may suppress this inhibitory effect, thereby indirectly allowing a thermogenic effect when an amino acid load is presented to the body.[111 112] This hypothesis is supported by the observation that the thermogenic effect of orally ingested amino acids increases in tetraplegic patients, whose neural connection between the central thermosensors and the periphery are severed.[1] Nonetheless, the combination of increased systemic vascular resistance coupled with the increased myocardial demand from the amino acid-induced thermogenesis may be potentially hazardous in patients at high risk of myocardial ischaemia. The role of such amino acid infusions in these higher-risk patients remains to be established.[23]

Post-anaesthetic shivering

Post-anaesthetic shivering is a common complication of modern anaesthesia, affecting 5–65% of patients after general anaesthesia and 33% of patients during epidural regional anaesthesia.[30] It is usually defined as readily detectable fasciculation or tremor of the face, jaw, head, trunk or extremities lasting longer than 15 s.[139] Apart from the obvious discomfort, post-anaesthetic shivering, like hypothermia, is associated with a number of potentially deleterious sequelae. These include increased oxygen consumption and carbon dioxide production,[26 71] catecholamine release,[26] increased cardiac output, tachycardia and hypertension,[4 119] and raised intraocular pressure.[90] Shivering may also decrease mixed venous oxygen saturation,[74] as well as interfering with monitoring.[34]

Post-anaesthetic shivering is often preceded by core hypothermia and vasoconstriction,[119] but not necessarily so.[30 54 56 137] Close observation of post-anaesthetic shivering, later aided by electromyographic studies, revealed that it is composed of two distinct patterns of muscular activity: a tonic pattern with 4–8 cycles min^{-1}, resembling thermoregulatory shivering and a clonic pattern, 5–7 Hz, consistent with uninhibited spinal reflexes.[108 119 129] An audit of over 2500 postoperative patients indicated that male gender, anticholinergic premedication, mode of ventilatory support and induction agents were risk factors for post-anaesthetic shivering, whilst the intraoperative use of pethidine virtually abolished shivering.[31] The use of propofol reduces the incidence of post-anaesthetic shivering as compared to thiopental.[126] Premedication with the muscarinic antagonists, atropine or glycopyrrolate, predisposes to post-anaesthetic shivering. If one accepts that glycopyrrolate penetrates the blood–brain barrier to a lesser degree than atropine, the efficacy of glycopyrrolate would point to a peripheral mechanism of action, possibly by peripheral vasodilation and increased heat loss prior to the induction of anaesthesia.[3]

Treatment of post-anaesthetic shivering

Post-anaesthetic shivering should not be treated in isolation from perioperative hypothermia. Not all patients who shiver are hypothermic, but many are, and successful treatment of shivering in this group without concomitant treatment of the hypothermia may result in deepening hypothermia.[69 122] A number of the physical methods of treating hypothermia have been shown to reduce the incidence of shivering, in particular forced-air patient warming systems,[77] and radiant heaters.[46 124] Radiant heaters work without increasing core temperature, perhaps by increasing the afferent warm input from the skin of the head and thorax. The mainstay of treatment of postoperative shivering is, however, pharmacological.

A wide range of drugs, including pethidine, other opioids (fentanyl, alfentanil, sufentanil, buprenorphine), doxapram, methylphenidate, clonidine and ketanserin, have all been reported to be effective in suppressing established shivering, and it would be surprising if all worked on a single part of the thermoregulatory mechanism. Pethidine, in particular, is remarkably effective in treating postoperative shivering,[2 25 57 83 87 89 99 140 141] 25 mg being sufficient when given intravenously to stop shivering in the majority of adults. When given in the presence of high-dose naloxone, which antagonizes both μ and κ opioid receptors, pethidine failed to reduce shivering or oxygen consumption, in contrast to its use in combination with low-dose naloxone,[83] suggesting that pethidine exerts its thermoregulatory effects via κ receptors. Pethidine and alfentanil, while reducing the shivering threshold, have been shown not to reduce the gain or maximum intensity of shivering, suggesting that pethidine's efficacy is due to the reduction in the shivering threshold.[64] However, alfentanil, which also decreases the shivering threshold,[78] is less effective than pethidine in treating post-anaesthetic shivering.[87 140]

As stated above, Solliman and Gillies[129] suggested that post-anaesthetic shivering may be due to differential recovery of the brain and spinal cord from anaesthesia, the latter recovering first, resulting in uninhibited spinal clonic tremor, perceived as shivering. Consistent with this hypothesis, doxapram, a cerebral stimulant commonly used as a respiratory stimulant, has also been shown to be effective against shivering, though not as effective as pethidine.[125 141]

Various drugs whose role is less easy to explain are also effective. Physostigmine, the anticholinesterase agent used for reversal of neuromuscular blockade, has been shown to be effective in preventing the onset of post-anaesthetic shivering.[57] This may explain in part why patients who undergo intermittent positive pressure ventilation during anaesthesia shiver less than those who breathe spontaneously,[31] and may imply that cholinergic pathways are involved in the thermoregulatory mechanisms that lead to shivering. Clonidine reduces the thresholds for both shivering and vasoconstriction; is effective in treating established post-anaesthetic shivering;[35 72] has been shown to be effective in suppressing shivering after extradural analgesia in parturients;[20] and given at induction of anaesthesia, will also prevent post-anaesthetic shivering without influencing core and peripheral temperature distribution.[16] The serotonergic antagonist ketanserin reduces established post-anaesthetic shivering,[72] and ondansetron at induction has recently been shown to prevent it, suggesting a role for serotonergic pathways in thermoregulatory control.[105]

Conclusions

Mild perioperative hypothermia is an extremely common but not trivial consequence of induction of anaesthesia, both general and regional. It results from impairment of the physiological set-point, such that the threshold for activation of thermoregulatory effector mechanisms (vasoconstriction and shivering) is reduced to much colder temperatures than would be tolerated in the conscious state. Although regional anaesthesia reduces these thresholds to a lesser extent than general anaesthesia, it more commonly reduces the gain and maximum intensity of the effector responses. Vasodilation induced by anaesthetic agents results in a core-to-peripheral redistribution of body heat, with initial, rapid core hypothermia, followed by a gradual, more linear further decrease in core temperature as heat is lost from the skin, maintaining the core-to-peripheral temperature gradient. When the skin vasoconstriction mechanism finally is activated, skin heat loss decreases and a steady-state situation arises where heat loss is balanced by ongoing metabolic heat production, reduced by only 20% during anaesthesia. Combined general–epidural anaesthesia is a particular risk factor for core hypothermia, as lower limb vasoconstriction, quantitatively the largest part of the peripheral thermal buffer, cannot occur due to the effects of the regional block. On emergence from anaesthesia, normal thresholds are restored, hence hypothermic patients may shiver, which causes a considerable metabolic challenge. The neurotransmitter pathways involved in the control of shivering are complex and involve a number of systems, evidenced by the variety of therapeutic agents that are effective in suppressing it.

The effects of perioperative hypothermia are almost exclusively undesirable. Prevention of perioperative hypothermia and post-anaesthetic shivering, which should be considered and managed as two components of the same syndrome, demonstrably improves the outcome in terms of reduced cardiac morbidity and blood loss, improved wound healing and shorter hospital stay. The known effects of hypothermia on drug metabolism and coagulation are also obviated and studies are indicated to establish the role of perioperative thermoregulation on postoperative myocardial ischaemia. Core temperature monitoring, accompanied by passive and active methods to maintain normothermia, should be part of routine intraoperative monitoring. This is especially so for patients at high risk of perioperative hypothermia, particularly patients undergoing body-cavity surgery, surgery greater than 1 h duration, children, the elderly and cases where combined general–epidural anaesthesia is being conducted. Wider awareness of the benefits of maintaining normothermia perioperatively has the potential to improve the quality of patient care and shorten hospital stay.

References

1 Aksnes AK, Brundin T, Hjeltnes N, Maehlum S, Wahren J. Meal-induced rise in resting energy expenditure in patients with complete cervical spinal cord lesions. *Paraplegia* 1993; **31**: 462–72

2 Alfonsi P, Hongnat JM, Lebrault C, Chauvin M. The effects of pethidine, fentanyl and lignocaine on postanaesthetic shivering. *Anaesthesia* 1995; **50**: 214–7

3 Baxendale BR, Mahajan RP, Crossley AW. Anticholinergic premedication influences the incidence of postoperative shivering. *Br J Anaesth* 1994, **72**: 291–4

4 Bay J, Nunn JF, Prys-Roberts C. Factors influencing arterial PO_2 during recovery from anaesthesia. *Br J Anaesth* 1968; **40**: 398–407

5 Belani K, Sessler DI, Sessler AM, *et al.* Leg heat content continues to decrease during the core temperature plateau in humans anesthetized with isoflurane. *Anesthesiology* 1993; **78**: 856–63

6 Bennett J, Ramachandra V, Webster J, Carli F. Prevention of hypothermia during hip surgery: effect of passive compared with active skin surface warming. *Br J Anaesth* 1994; **73**: 180–3

7 Benzinger TH. Heat regulation: homeostasis of central temperature in man. *Physiol Revs* 1969; **49**: 671–759

8 Benzinger TH. Clinical temperature. New physiological basis. *JAMA* 1969; **209**. 1200–6

9 Bissonnette B, Sessler DI, LaFlamme P. Intraoperative temperature monitoring sites in infants and children and the effect of inspired gas warming on esophageal temperature. *Anesth Analg* 1989; **69**: 192–6

10 Bligh J, Johnson KG. Glossary of terms for thermal physiology. *J Appl Physiol (Lond)* 1973; 35. 941–61

11 Boulant JA, Bignall KE Hypothalamic neuronal responses to peripheral and deep-body temperatures. *Am J Physiol* 1973; **225**: 1371–4

12 Boulant JA, Demieville HN. Responses of thermosensitive preoptic and septal neurons to hippocampal and brain stem stimulation. *J Neurophysiol* 1977; **40**: 1356–68

13 Boulant JA, Gonzalez RR. The effect of skin temperature on the hypothalamic control of heat loss and heat production *Brain Res* 1977; **120**: 367–72

14 Boulant JA, Hardy JD. The effect of spinal and skin temperatures on the firing rate and thermosensitivity of preoptic neurones. *J Physiol* 1974; **240**. 639–60

15 Buggy D, Gardiner J The space blanket and shivering during extradural analgesia in labour. *Acta Anesthesiol Scand* 1995; **39**: 551–3

16 Buggy D, Higgins P, Moran C, O'Donovan F, McCarroll M. Clonidine at induction reduces shivering after general anaesthesia. *Can J Anaesth* 1997; **44**: 263–7

17 Buggy D, Hughes N. Pre-emptive use of the space blanket reduces shivering after general anaesthesia. *Br J Anaesth* 1994; **72**: 393–6

18 Cabanac M, Stolwijk JA, Hardy JD. Effect of temperature and pyrogens on single-unit activity in the rabbit's brain stem. *J Appl Physiol* 1968; **24**: 645–52

19 Campbell IT. Thermoregulation in critical illness. *Br J Anaesth* 1997; **78**: 121–2

20 Capogna G, Celleno D IV clonidine for post-extradural shivering in parturients. a preliminary study. *Br J Anaesth* 1993; **71**. 294–5

21 Carli F, Emery PW, Freemantle CA Effect of preoperative normothermia on postoperative protein metabolism in elderly patients undergoing hip arthroplasty. *Br J Anaesth* 1989, **63**: 276–82

22 Carli F, Halliday D. Continuous epidural blockade arrests the postoperative decrease in muscle protein fractional synthetic rate in surgical patients *Anesthesiology* 1997; **86**: 1033–40

23 Carli F, MacDonald IA. Perioperative inadvertent hypothermia: what do we need to prevent? *Br J Anaesth* 1996, **76** 601–3

24 Carli F, Webster J, Pearson M, *et al.* Postoperative protein metabolism: effect of nursing elderly patients for 24 h after abdominal surgery in a thermoneutral environment. *Br J Anaesth* 1991; **66**: 292–9

25 Casey WF, Smith CE, Katz JM, O'Loughlin K, Weeks SK. Intravenous meperidine for control of shivering during caesarean section under epidural anaesthesia *Can J Anaesth* 1988, **35**: 128–33

26 Ciofolo MJ, Clergue F, Devilliers C, Ben Ammar M, Viars, P. Changes in ventilation, oxygen uptake, and carbon dioxide output during recovery from isoflurane anesthesia. *Anesthesiology* 1989, **70**: 737–41

27 Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *New Engl J Med* 1992, **326**: 281–6

28 Colin J, Timbal J, Houdas Y, Boutelier C, Guieu JD Computation of mean body temperature from rectal and skin temperature. *J Appl Physiol* 1971; **31**. 484–9

29 Cork RC, Vaughan RW, Humphrey LS Precision and accuracy of intraoperative temperature monitoring *Anesth Analg* 1983; **62**: 211–4

30 Crossley AW. Peri-operative shivering. *Anaesthesia* 1992; **47**. 193–5

31 Crossley AW. Six months of shivering in a district general hospital. *Anaesthesia* 1992; **47**: 845–8

32 Dawkins MJ, Scopes JW. Non-shivering thermogenesis and brown adipose tissue in the human new-born infant. *Nature* 1965; **206**: 201–2

33 Deacock S, Holdcroft A. Heat retention using passive systems during anaesthesia: comparison of two plastic wraps, one with reflective properties. *Br J Anaesth* 1997; **79**. 766–9

34 Decourcy JG, Eldred C. Artefactual hypotension from shivering *Anaesthesia* 1989; **44**: 787–8

35 Delaunay L, Bonnet F, Liu N, Beydon L, Catoire P, Sessler DI. Clonidine comparably decreases the thermoregulatory thresholds for vasoconstriction and shivering in humans. *Anesthesiology* 1993; **79**: 470–4

36 Dickenson AH. Specific responses of rat raphe neurones to skin temperature *J Physiol (Lond.)* 1977; **273**: 277–93

37 Douning LK, Ramsay MA, Swygert TH, *et al.* Temperature corrected thrombelastography in hypothermic patients *Anesth Analg* 1995; **81**: 608–11

38 Downey JA, Chiodi HP, Darling RC. Central temperature regulation in the spinal man. *J Appl Physiol* 1967; **22**: 91–4

39 Downey JA, Mottram RF, Pickering GW. The location by regional cooling of central temperature receptors in the conscious rabbit *J Physiol (Lond)* 1964; **170**: 415–9

40 DuBois D, DuBois EF. The measurement of the surface area of man. *Arch Int Med* 1915, **15**: 868–73

41 Emerick TH, Ozaki M, Sessler DI, Walters K, Schroeder M. Epidural anesthesia increases apparent leg temperature and decreases the shivering threshold. *Anesthesiology* 1994, **81**. 289–98

42 Frank SM, Beattie C, Christopherson R, *et al.* Unintentional hypothermia is associated with postoperative myocardial ischemia. The Perioperative Ischemia Randomized Anesthesia Trial Study Group. *Anesthesiology* 1993, **78** 468–76

43 Frank SM, Higgins MS, Breslow MJ, *et al.* The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia. A randomized clinical trial. *Anesthesiology* 1995; **82**: 83–93

44 Frank SM, Fleisher LA, Breslow MJ *et al.* Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. *JAMA* 1997; 277: 1127–34

45 Giesbrecht GG, Ducharme MB, McGuire JP. Comparison of forced-air patient warming systems for perioperative use. *Anesthesiology* 1994; **80**: 671–9

46 Giesecke A, Sharkey A, Murphy M, Rice L, Lipton J. Control of postanesthetic shivering with radiant-heat. *Acta Anesthesiol Scand* 1987; **31**: 28

47 Glosten B, Sessler DI, Ostman LG, Faure EA, Karl L, Thisted RA Intravenous lidocaine does not cause shivering-like tremor or alter thermoregulation. *Reg Anesth* 1991; **16**: 218–22

48 Guyton AC. Body temperature, temperature regulation and fever. In: Guyton AC, Hall JE, eds. *Textbook of Medical Physiology*, 9th edition. Philadelphia: W.B. Saunders, 1996; 911–22

49 Hanagata K, Matsukawa T, Sessler DI *et al.* Isoflurane and sevoflurane produce a dose-dependent reduction in the shivering threshold in rabbits. *Anesth Analg* 1995; 81: 581–4

50 Hardy JD. Physiology of temperature regulation. *Physiol Rev* 1961; **41**: 521–86

51 Hardy JD, Hellon RF, Sutherland K. Temperature sensitive neurones in the dog's hypothalamus. *J Physiol (Lond)* 1964; **175**: 242–5

52 Heier T, Caldwell JE, Sessler DI, Miller RD. Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. *Anesthesiology* 1991; **74**: 815–9

53 Hervey GR. Thermoregulation. In: Emslie-Smith D, Paterson C, Scratcherd T, Read N, eds. *Textbook of Physiology*, 11th edition. Edinburgh: Churchill-Livingstone, 1988; 510–33

54 Holdcroft A, Hall GM. Heat loss during anaesthesia. *Br J Anaesth* 1978; **50**: 157–64

55 Holdcroft A, Hall GM, Cooper GM. Redistribution of body heat during anaesthesia. A comparison of halothane, fentanyl and epidural anaesthesia. *Anaesthesia* 1979; **34**: 758–64

56 Horn EP, Sessler DI, Standl T, *et al.* Non-thermoregulatory shivering in patients recovering from isoflurane or desflurane anesthesia. *Anesthesiology* 1998; **89**: 878–86

57 Horn EP, Standl T, Sessler DI, von Knobelsdorff G, Buchs C, Schulte am Esch J. Physostigmine prevents postanesthetic shivering as does meperidine or clonidine. *Anesthesiology* 1998; **88**: 108–13

58 Hynson J, Sessler DI, Moayeri A. The effects of pre-induction warming on temperature and blood pressure during propofol-nitrous oxide anesthesia *Anesthesiology* 1993; **79**: 219–24

59 Hynson JM, Sessler DI. Intraoperative warming therapies: a comparison of three devices. *J Clin Anesth* 1992; **4**. 194–9

60 Hynson JM, Sessler DI, Belani K, *et al.* Thermoregulatory vasoconstriction during propofol/nitrous oxide anesthesia in humans: threshold and oxyhemoglobin saturation. *Anesth Analg* 1992; **75**: 947–52

61 Hynson JM, Sessler DI, Glosten B, McGuire J. Thermal balance and tremor patterns during epidural anesthesia. *Anesthesiology* 1991, **74**: 680–90

62 Ikeda T, Kim JS, Sessler DI, Negishi C, Turakhia M, Jeffrey R. Isoflurane alters shivering patterns and reduces maximum shivering intensity. *Anesthesiology* 1998; **88**: 866–73

63 Ikeda T, Sessler DI, Kikura M, Kazama T, Ikeda K, Sato S. Less core hypothermia when anesthesia is induced with inhaled sevoflurane than with intravenous propofol. *Anesth Analg* 1999, **88**: 921–4

64 Ikeda T, Sessler DI, Tayefeh F, *et al.* Meperidine and alfentanil do not reduce the gain or maximum intensity of shivering. *Anesthesiology* 1998; **88**: 858–65

65 Inoue S, Murakami N. Unit responses in the medulla oblongata of rabbit to changes in local and cutaneous temperature. *J Physiol (Lond.)* 1976; **259**: 339–56

66 Iwashita H, Matsukawa T, Ozaki M, Sessler DI, Imamura M, Kumazawa T. Hypoxemia decreases the shivering threshold in rabbits anesthetized with 0.2 minimum alveolar anesthetic concentration isoflurane. *Anesth Analg* 1998; **87**: 1408–11

67 Jacobson FH, Squires RD. Thermoregulatory responses of the cat to preoptic and environmental temperatures. *Am J Physiol* 1970; **218**: 1575–82

68 Jessen C, Feistkorn G. Some characteristics of core temperature signals in the conscious goat. *Am J Physiol* 1984; **247**: R456–64

69 Johnson MD, Sevarino FB, Lema MJ. Cessation of shivering and hypothermia associated with epidural sufentanil. *Anesth Analg* 1989; **68**: 70–1

70 Johnston TD, Chen Y, Reed RL, II. Functional equivalence of hypothermia to specific clotting factor deficiencies. *Trauma* 1994; **37**: 413–7

71 Jones HD, McLaren CAB. Postoperative shivering and hypoxaemia after halothane, nitrous oxide and oxygen anaesthesia. *Br J Anaesth* 1965; **37**: 35–41

72 Joris J, Banache M, Bonnet F, Sessler DI, Lamy M. Clonidine and ketanserin both are effective treatment for postanesthetic shivering. *Anesthesiology* 1993; **79**: 532–9

73 Joris J, Ozaki M, Sessler DI, *et al.* Epidural anesthesia impairs both central and peripheral thermoregulatory control during general anesthesia. *Anesthesiology* 1994; **80**: 268–77

74 Kaplan JA, Guffin AV. Shivering and changes in mixed venous oxygen saturation after cardiac surgery. *Anesth Analg* 1985; **64**: 235–9

75 Kim JS, Ikeda T, Sessler DI, Turakhia M, Jeffrey R. Epidural anesthesia reduces the gain and maximum intensity of shivering. *Anesthesiology* 1998; **88**: 851–7

76 Kluger MJ. Temperature regulation, fever, and disease. *Int Rev Physiol* 1979; **20**: 209–51

77 Krenzischek DA, Frank SM, Kelly S. Forced-air warming versus routine thermal care and core temperature measurement sites. *J Postgrad Anesth Nursing* 1995; **10**: 69–78

78 Kurz A, Go JC, Sessler DI, Kaer K, Lanson MD, Bjorketen AR. Alfentanil slightly increases the sweating threshold and markedly reduces the vasoconstriction and shivering thresholds. *Anesthesiology* 1995; **83**: 293–9

79 Kurz A, Plattner O, Sessler DI, Huemer G, Redl G, Lackner F. The threshold for thermoregulatory vasoconstriction during nitrous oxide/isoflurane anesthesia is lower in elderly than in young patients. *Anesthesiology* 1993; **79**: 465–9

80 Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *New Engl J Med* 1996; **334**: 1209–15

81 Kurz A, Sessler DI, Schroeder M, Kurz M. Thermoregulatory response thresholds during spinal anesthesia. *Anesth Analg* 1993; **77**: 721–6

82 Kurz A, Xiong J, Sessler DI, Dechert M, Noyes K, Belani K. Desflurane reduces the gain of thermoregulatory arteriovenous shunt vasoconstriction in humans. *Anesthesiology* 1995; **83**: 1212–9

83 Kurz M, Belani KG, Sessler DI, Lanson MD. Naloxone, meperidine, and shivering. *Anesthesiology* 1993; **79**: 1193–201

84 Lenhardt R, Marker E, Goll V, *et al.* Mild intraoperative hypothermia prolongs postanesthetic recovery. *Anesthesiology* 1997; **87**: 1318–23

85 Leslie K, Sessler DI, Bjorksten AR, Moayeri A. Mild hypothermia alters propofol pharmacokinetics and increases the duration of action of atracurium. *Anesth Analg* 1995; **80**: 1007–14

86 Lindahl SG. Sensing cold and producing heat. *Anesthesiology* 1997; **86**. 758–9

87 Lyons B, Carroll M, McDonald NJ. The treatment of postanaesthetic shivering: a double blind comparison between alfentanil and pethidine *Acta Anesthesiol Scand* 1995; **39**: 979–8

88 Lyons B, Taylor A, Power C, Casey W. Postanaesthetic shivering in children. *Anaesthesia* 1996; **51**: 442–5

89 Macintyre PE, Pavlin EG, Dwersteg JF. Effect of meperidine on oxygen consumption, carbon dioxide production, and respiratory gas exchange in postanesthesia shivering. *Anesth Analg* 1987; **66**: 751–5

90 Mahajan RP, Grover VK, Sharma SL, Singh H. Intraocular pressure changes during muscular hyperactivity after general anesthesia. *Anesthesiology* 1987; **66**: 419–21

91 Matsukawa T, Hanagata K, Ozaki M, Ivashita H, Koshimizu M, Kumazawa T. I.m midazolam as premedication produces a concentration-dependent decrease in core temperature in male volunteers. *Br J Anaesth* 1997; **78**: 396–9

92 Matsukawa T, Sessler DI, Christensen R, Ozaki M, Schroeder M. Heat flow and distribution during epidural anesthesia. *Anesthesiology* 1995; **83**· 961–7

93 Matsukawa T, Sessler DI, Ozaki M, *et al.* Comparison of distal oesophageal temperature with 'deep' and tracheal temperatures. *Can J Anaesth* 1997; **44**: 433–8

94 Matsukawa T, Sessler DI, Sessler AM, *et al* Heat flow and distribution during induction of general anesthesia. *Anesthesiology* 1995, **82**: 662–73

95 Miller RD. Pharmacokinetics of competitive muscle relaxants. *Br J Anaesth* 1982; **54**: 161–7

96 Morris RH, Kumar A. The effect of warming blankets on maintenance of body temperature of the anesthetized, paralyzed adult patient *Anesthesiology* 1972; **36**. 408–11

97 Nakayama T, Hardy JD. Unit responses in the rabbit's brain stem to changes in brain and cutaneous temperature. *J App Physiol* 1969; **27**: 848–57

98 Ozaki M, Kurz A, Sessler DI, *et al.* Thermoregulatory thresholds during epidural and spinal anesthesia. *Anesthesiology* 1994; **81**: 282–8

99 Pauca AL, Savage RT, Simpson S, Roy RC. Effect of pethidine, fentanyl and morphine on post-operative shivering in man *Acta Anesthesiol Scand* 1984; **28**: 138–43

100 Pierau FK, Wurster RD. Primary afferent input from cutaneous thermoreceptors. *Fed Proc* 1981; **40**: 2819–24

101 Plattner O, Semsroth M, Sessler DI, *et al.* Lack of nonshivering thermogenesis in infants anesthetized with fentanyl and propofol. *Anesthesiology* 1997; **86**: 772–7

102 Ponte J, Collett BJ, Walmsley A. Anaesthetic temperature and shivering in epidural anaesthesia *Acta Anesthesiol Scand* 1986; **30**. 584–7

103 Ponte J, Sessler DI. Extradurals and shivering: effects of cold and warm extradural saline injections in volunteers *Br J Anaesth* 1990; **64**. 731–3

104 Poulos DA Central processing of cutaneous temperature information. *Fed Proc* 1981; **40**. 2825–9

105 Powell RM, Buggy DJ. Ondansetron at induction reduces shivering after general anaesthesia *Anesth Analg* 2000; **90**: in press

106 Puhakka K, Anttonen H, Niskanen J, Ryhanen P. Calculation of mean skin temperature and changes in body heat content during paediatric anaesthesia *Br J Anaesth* 1994; **72**: 548–53

107 Ramanathan NL. A new weighting system for mean surface temperature of the human body. *J Appl Physiol* 1964; **19**: 531–3

108 Rosenberg H, Clofine R, Bialik O Neurologic changes during awakening from anesthesia. *Anesthesiology* 1981; **54**: 125–31

109 Schmied H, Kurz A, Sessler DI, Kozek S, Reiter A. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty *Lancet*, 1996, **347**. 289–92

110 Sellden E, Branstrom R, Brundin T Preoperative infusion of amino acids prevents postoperative hypothermia *Br J Anaesth* 1996; **76**· 227–34

111 Sellden E, Brundin T, Wahren J Augmented thermic effect of amino acids under general anaesthesia: a mechanism for prevention of anaesthesia-induced hypothermia *Clin Sci* 1994, **86**. 611–8

112 Sellden E, Branstrom R, Brundin T. Augmented thermic effect of amino acids under general anaesthesia occurs predominantly in extra-splanchnic tissues. *Clin Sci* 1996; **91**. 431–9

113 Sessler DI Temperature monitoring In: Millar RD, ed. *Anesthesia* New York: Churchill Livingstone, 1994; 1363–82

114 Sessler DI. Perianesthetic thermoregulation and heat balance in humans. *FASEB J* 1993; **7** 638–44

115 Sessler DI. Central thermoregulatory inhibition by general anaesthesia. *Anesthesiology* 1991; **75**: 557–9

116 Sessler DI, McGuire J, Hynson J, Moayeri A, Heier T Thermoregulatory vasoconstriction during isoflurane anesthesia minimally decreases cutaneous heat loss *Anesthesiology* 1992, **76**· 670–5

117 Sessler DI, Moayeri A, Stoen R, Glosten B, Hynson J, McGuire J. Thermoregulatory vasoconstriction decreases cutaneous heat loss. *Anesthesiology* 1990; **73**. 656–60

118 Sessler DI, Ponte J Shivering during epidural anesthesia *Anesthesiology* 1990, **72**: 816–21

119 Sessler DI, Rubinstein EH, Moayeri A Physiologic responses to mild perianesthetic hypothermia in humans. *Anesthesiology* 1991, **75**: 594–610

120 Sessler DI, Schroeder M. Heat loss in humans covered with cotton hospital blankets. *Anesth Analg* 1993; **77** 73–7

121 Sessler DI, Schroeder M, Merrifield B, Matsukawa T, Cheng C Optimal duration and temperature of prewarming *Anesthesiology* 1995; **82**: 674–81

122 Sevarino FB, Johnson MD, Lema MJ, Datta S, Ostheimer GW, Naulty JS. The effect of epidural sufentanil on shivering and body temperature in the parturient. *Anesth Analg* 1989; **68**: 530–3

123 Shanks CA Mean skin temperature during anaesthesia an assessment of formulae in the supine surgical patient *Br J Anaesth* 1975; **47**: 871–5

124 Sharkey A, Lipton JM, Murphy MT, Giesecke AH. Inhibition of postanesthetic shivering with radiant heat. *Anesthesiology* 1987, **66**: 249–52

125 Singh P, Dimitriou V, Mahajan RP, Crossley AW. Double-blind comparison between doxapram and pethidine in the treatment of postanaesthetic shivering. *Br J Anaesth* 1993; **71**: 685–8

126 Singh P, Harwood R, Cartwright DP, Crossley AW. A comparison of thiopentone and propofol with respect to the incidence of postoperative shivering *Anaesthesia* 1994; **49**. 996–8

127 Slotman GJ, Jed EH, Burchard KW. Adverse effects of hypothermia in postoperative patients. *Am J Surg* 1985; **149** 495–501

128 Smith CE, Gerdes E, Sweda S, *et al.* Warming intravenous fluids reduces perioperative hypothermia in women undergoing ambulatory gynecological surgery. *Anesth Analg* 1998, **87**· 37–41

129 Soliman MG, Gillies DM. Muscular hyperactivity after general anaesthesia *Can Anaesth Soc J* 1972, **19**· 529–35

130 Squires RD. Thermoregulatory effects of injections of gamma amino butyric acid (GABA) and picrotoxin into medial preoptic region of cats. *Fed Proc* 1967; **26**: 555–9

131 Squires RD, Jacobson FH. Chronic deficits of temperature regulation produced in cats by preoptic lesions. *Am J Physiol* 1968; **214**: 549–60

132 Stoen R, Sessler DI. The thermoregulatory threshold is inversely proportional to isoflurane concentration. *Anesthesiology* 1990; **72**: 822–7

133 Todd MM, Warner DS. A comfortable hypothesis reevaluated. Cerebral metabolic depression and brain protection during ischemia. *Anesthesiology* 1992; **76**: 161–4

134 Vale RJ. Cooling during vascular surgery. *Br J Anaesth* 1972; **44**: 1334

135 Valeri CR, Khabbaz K, Khuri SF, *et al.* Effect of skin temperature on platelet function in patients undergoing extracorporeal bypass. *J Thorac Cardiovasc Surg* 1992; **104**: 108–16

136 Van Oss CJ, Absolom DR, Moore LL, Park BH, Humbert JR. Effect of temperature on the chemotaxis, phagocytic engulfment, digestion and O_2 consumption of human polymorphonuclear leukocytes. *J Reticuloendothelial Soc* 1980; **27**: 561–5

137 Vaughan MS, Vaughan RW, Cork RC. Postoperative hypothermia in adults: relationship of age, anesthesia, and shivering to rewarming. *Anesth Analg* 1981; **60**: 746–51

138 Washington DE, Sessler DI, Moayeri A, *et al.* Thermoregulatory responses to hyperthermia during isoflurane anesthesia in humans. *J Appl Physiol* 1993; **74**: 82–7

139 Webb PJ, James FM III, Wheeler AS Shivering during epidural analgesia in women in labor. *Anesthesiology* 1981; **55**: 706–7

140 Wrench IJ, Cavill G, Ward JE, Crossley AW. Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering. *Br J Anaesth* 1997; **79**: 541–2

141 Wrench IJ, Singh P, Dennis AR, Mahajan RP, Crossley AW. The minimum effective doses of pethidine and doxapram in the treatment of post-anaesthetic shivering. *Anaesthesia* 1997; **52**: 32–6

142 Wyss CR, Brengelmann GL, Johnson JM, Rowell LB, Silverstein D. Altered control of skin blood flow at high skin and core temperatures. *J Appl Physiol* 1975; **38**: 839–45

British Journal of Anaesthesia 84 (5) 629–31 (2000)

BJA

SHORT COMMUNICATIONS

Reduced cerebral embolic signals in beating heart coronary surgery detected by transcranial Doppler ultrasound†

M. P. R. Watters[1]*, A. M. Cohen,[1] C. R. Monk[1], G. D. Angelini[2] and I. G. Ryder[1]

[1]Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary, Marlborough Street, Bristol BS2 8HW and [2]Bristol Heart Institute, Bristol Royal Infirmary, Marlborough Street, Bristol BS2 8HW, UK

**Corresponding author*

Cerebral emboli detected by transcranial Doppler imaging were recorded in 20 patients undergoing multiple-vessel coronary artery bypass surgery, either with or without cardiopulmonary bypass, in a prospective unblinded comparative study. Emboli were recorded continuously from the time of pericardial incision until 10 min after the last aortic instrumentation. The numbers of coronary grafts and of aortic clampings were also documented. Patients undergoing revascularization with cardiopulmonary bypass had more emboli (median 79, range 38–876) per case compared with patients having off-pump surgery (median 3, range 0–18). No clinically detectable neurological deficits were seen in either group. Beating heart surgery is associated with fewer emboli than coronary surgery with cardiopulmonary bypass. Further research is necessary to determine whether a smaller number of emboli alters the incidence of neurological deficit after cardiac surgery.

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Keywords: brain, cortex, cerebral; embolism; measurement techniques, Doppler ultrasound; monitoring; surgery, cardiovascular

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Cerebral complications cause considerable morbidity after cardiac surgery, with an incidence of stroke between 1 and 6% and of more subtle neuropsychological changes between 20 and 40%.[1] Although many factors contribute to the neurological outcome, large numbers of emboli detected by transcranial Doppler (TCD) imaging during cardiac surgery with cardiopulmonary bypass (CPB) are known to be associated with more neurological deficits.[2 3] Clarke and co-workers suggested that the number of cerebral emboli detected with TCD is a useful intermediate endpoint in evaluating new surgical techniques with respect to the neurological outcome.[2] Multiple-vessel off-pump coronary artery bypass grafting (OPCAB) on a beating heart is an increasingly common procedure. In this study we describe the frequency of right middle cerebral artery emboli detected by TCD in patients undergoing multiple vessel coronary artery bypass grafts (CABG) with or without CPB.

Methods and results

After we had obtained ethical approval and patient consent, we studied 20 patients undergoing CABG with or without CPB. Patients without a suitable acoustic bone window for TCD were not included in the study. The choice of operation was at the surgeon's discretion. None of the patients had radiographic evidence of calcification of the proximal aorta. All patients received fentanyl 15–20 mg kg^{-1} and an infusion of propofol 3 mg kg^{-1} h^{-1} The lungs were ventilated with an oxygen–air mixture to keep blood oxygen saturation Sp_{O_2} above 94%. Arterial Pa_{CO_2} was maintained between 35 and 40 mm Hg. Metaraminol boluses 0.5 mg were given if blood pressure fell by more than 10% from baseline.

After induction of anaesthesia, a 2-mHz bidirectional transcranial Doppler probe (Sci Med, Bristol, UK) was positioned over the right temple until an adequate signal was obtained from the proximal segment of the right middle cerebral artery. The probe was kept in place by a purpose-built headband (Sci Med) maintaining the angle and depth of insonation. Flow velocity profiles were displayed continuously in real time. All patients were operated on through a median sternotomy.

In patients undergoing conventional CABG with CPB, a

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Table 1 Summary data for patient groups having CABG with CPB or without CPB (OPCAB) Data are mean (SD) unless otherwise stated

	CABG with CPB $n=10$	**OPCAB** $n=10$
Age (range) (yr)	61 (47–69)	60 (48–70)
Sex	10 M	8 M, 2 F
Body mass index	27.61 (3 72)	27 34 (3.25)
Lowest nasopharyngeal temperature intraoperatively	34.0 (0 56)	35 3 (0 69)*
Parsonnet score		
0–5	9	6
6–10	0	2
>10	1	2
Total no. grafts	29	27
Total no. aortic cross-clamps	10	0
Total no. partial aortic clampings	12	13
Time recorded (min)	123 (14.3)	105 (24 3)
Microembolus count (median and range)	79 (38–876)	3 (0–18)**

$^{*}P<0\ 05$; $^{**}P<0\ 001$.

transaortic cross-clamp was applied after establishment of CPB and intermittent warm-blood cardioplegia was administered into the aortic root. CPB was with non-pulsatile flow, a membrane oxygenator (Bard, Haverhill, MA, USA) and a 40-μm in-line arterial filter (Bard). Alpha stat pH management was used during CPB, and nasopharyngeal temperature was maintained between 34 and 37°C. The cross-clamp was removed on completion of distal anastomoses and an aortic side-biting clamp was applied in order to perform the proximal anastomoses.

For the OPCAB patients, distal anastomoses were performed on the beating heart after the heart had been positioned and stabilized with a purpose-made retractor. After completion of each distal anastomosis, the heart was returned to its native position and an aortic side biting clamp applied to perform the proximal anastomosis.

Embolic signals were identified with TCD by a well-recognized[4] combination of a sudden change in the acoustic density of the signal, visible as an instantaneous bright signal on the visual display, and a characteristic high-frequency audible response similar to a chirping or whistling sound. Counts of emboli were recorded continuously by one of the investigators (MW) during the period from pericardial incision until 10 min after the last aortic manipulation. In the OPCAB group, this was after the last removal of the aortic side-biting clamp, whereas in the CPB group this was after removal of the aortic cannula. The number of aortic clampings in each group was recorded, as was the total time during which emboli were detected.

Counts of emboli were compared using the Mann–Whitney *U*-test. Continuous data were analysed using Student's *t*-test. A *P* value of <0.05 was considered statistically significant.

None of the OPCAB procedures were converted to CABG with CPB. No clinical neurological deficits were detected in either group. The results are summarized in Table 1.

Comment

In this study, patients undergoing multiple-vessel OPCAB had markedly fewer cerebral emboli, detected intraoperatively by TCD of the right middle cerebral artery, than patients undergoing CABG with CPB. This has not been reported previously for patients requiring multiple-vessel revascularization, who could have received CABG with CPB, although BhaskerRao and co-workers have shown similar results in a group of patients considered unsuitable for CPB, who had predominantly single-vessel grafting through a left minithoracotomy with no proximal aortic clamping.[5]

The incidence of emboli detected by TCD is known to be related to aortic instrumentation.[6] Although partial aortic clamping to perform proximal anastomoses is usually required in both on- and off-bypass coronary surgery, only with on-bypass surgery are a transaortic cross-clamp and aortic and cardioplegia cannulae required. In the patients undergoing CABG with CPB, although noticeable increases in embolic signals occurred during aortic instrumentations, embolic signals also occurred throughout the bypass period. The total number of emboli detected was similar to the numbers reported in previous studies in which a membrane oxygenator and a 40-μm in-line arterial filter were used.[7] The few emboli in the OPCAB group occurred only on removal of aortic side-biting clamps.

The study was unblinded and not randomized, and therefore the possibility of bias exists. However, all recordings were made continuously by a single observer, and emboli detected by TCD have a characteristic quality that is easy to recognize and difficult to misinterpret. Considering the magnitude of the difference in emboli counts, observer bias is unlikely to have affected the difference seen between the two groups. Secondly, although all patients could have received conventional CABG using CPB, patient selection for OPCAB is dictated by the anatomical position of the coronary lesions and surgical preference. It is possible, but unlikely, that this might have led to a difference in associated aortic atheroma between the two groups. The groups were likely to be similar, given the similar Parsonnet risk scores and the similar numbers of coronary grafts (Table 1), together with the absence of any calcification on preoperative chest x-ray or angiography. We consider it unlikely that possible differences in atheroma could significantly affect the large difference in emboli counts seen. Also, factors affecting cerebral blood flow, such as core temperature (which was actually higher in the off-bypass group), would be unlikely to affect the embolus counts to the degree observed.

We cannot conclude from this study that OPCAB surgery is associated with better neurological outcome. It is impossible using TCD to determine the nature of the emboli recorded. Gaseous emboli, for example, may pose less risk to the patient than solid atheroemboli dislodged during aortic manipulation. However, the finding that OPCAB surgery is associated with so few cerebral emboli warrants further investigation into whether OPCAB surgery is associated with less neurological deficit than CABG with CPB.

References

1 Mills SA. Risk factors for cerebral injury and cardiac surgery. *Ann Thorac Surg* 1995; **59**: 1296–9

2 Clark RE, Brillman J, Davis DA, Lovell MR, Price TR, Magovern GJ. Microemboli during coronary artery bypass grafting. Genesis and effect on outcome. *J Thorac Cardiovasc Surg* 1995; **109**: 249–57

3 Pugsley W, Klinger L, Paschalis C, Treasure T, Harrison M, Newman S. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke* 1994; **25**: 1393–9

4 Spencer MP. Detection of cerebral arterial emboli. In Newell DW, Aaslid R, eds. *Transcranial Doppler*. New York. Raven Press, 1992; 215–230

5 BhaskerRao B, VanHimbergen D, Edmonds HL Jr, *et al.* Evidence for improved cerebral function after minimally invasive bypass surgery *J Card Surg* 1998; **13**· 27–31

6 Barbut D, Hinton RB, Szatrowski TP, *et al.* Cerebral emboli detected during bypass surgery are associated with clamp removal. *Stroke* 1994; **25**: 2398–2402

7 Benaroia M, Baker AJ, Mazer CD, Erret L. Effect of aortic cannula characteristics and blood velocity on transcranial doppler-detected microemboli during cardiopulmonary bypass. *J Card Vasc Anaesth* 1998; **12**: 266–9

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Effects of isoflurane, sevoflurane and propofol anaesthesia on jugular venous oxygen saturation in patients undergoing coronary artery bypass surgery

Koichiroh Nandate[1] [2], Alain Vuylsteke[2], Indrek Ratsep[2], Souad Messahel[1]
Amo Oduro-Dominah[2], David K. Menon[1] and Basil F. Matta[3]*

[1]Department of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK. [2]Department of Anaesthesia, Papworth Hospital, Papworth Everand, Cambridge CB3 8RE, UK. [3]Department of Anaesthesia, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK

**Corresponding author*

We investigated the effect of sevoflurane, isoflurane and propofol on jugular venous bulb oxygen saturation (Sj_{O_2}) in 21 patients undergoing coronary artery bypass graft surgery (CABG) during and after normothermic cardiopulmonary bypass (CPB). Patients received a standardized anaesthetic consisting of fentanyl, midazolam and were then randomly allocated to receive either isoflurane, sevoflurane or propofol for maintenance. Sj_{O_2} values were significantly lower than baseline 1 h after CPB in the propofol but not the isoflurane or the sevoflurane groups. Furthermore, Sj_{O_2} values were significantly higher during CPB in the isoflurane group (P=0.0081) and significantly lower 6 h after CPB in the sevoflurane group (P=0.0447) when compared to the propofol group. We conclude that jugular venous desaturation during and after normothermic CPB is more likely during propofol anaesthesia.

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Jugular venous desaturation, common during cardiopulmonary bypass (CPB),[1–3] has been correlated with postoperative neuropsychiatric dysfunction.[3] Furthermore, the incidence of delayed jugular venous desaturation which was common early after hypothermic CPB was not attenuated by the supplemental propofol.[4] [5] The aim of this study was

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to investigate the temporal relationship between CPB and jugular venous desaturation during isoflurane, sevoflurane and propofol anaesthesia.

Methods and results

After Local Research Ethics Committee approval and informed written consent were obtained, 21 patients undergoing elective CABG were enrolled in the study. Patients were managed with a standardized normothermic CPB protocol and were allocated randomly to receive isoflurane, sevoflurane or propofol for maintenance of general anaesthesia (each group $n=7$). Patients with a history of neurological or cerebrovascular disease were excluded.

After premedication with morphine 15 mg and scopolamine 0.3 mg, anaesthesia was induced with midazolam 0.1 mg kg^{-1} and fentanyl 15 μg kg^{-1}, and maintained with 0.5–1.0% isoflurane, 1.5–2% sevoflurane or propofol 3 mg kg^{-1} h^{-1}. Neuromuscular blockade was achieved with pancuronium 0.1 mg kg^{-1} and the lungs were ventilated with an air/oxygen mixture, aiming for an arterial carbon dioxide tension (Pa_{CO_2}) of 35–40 mm Hg during mechanical respiratory support. Mean arterial pressure (MAP) was maintained above 50 mm Hg with volume loading and vasoactive agents (phenylephrine). In addition to the standard monitors for cardiac anaesthesia, a right jugular bulb catheter (Vygon Leader Cath 14G; Vygon, Gloucs, UK) was sited and its position confirmed radiographically. Blood sampled from the catheter was analysed for oxygen saturation using bench Co-Oximetry (Rapid lab ™ 860, Chiron Diagnostics, US) after induction of anaesthesia (T0, baseline), 30 min after starting (T1) and immediately after weaning from CPB (T2), and then at 1, 6, 12 and 18 h after CPB (T3, T4, T5 and T6 respectively).

Standard normothermic (36–7°C) non-pulsatile bypass with membrane oxygenation was used with α-stat management of Pa_{CO_2}. Perfusion pressure was maintained between 50 and 70 mm Hg by altering the concentration of the anaesthetic agent administered during CPB. Isoflurane (0.5–1.0%) or 1.5–2% sevoflurane were administered continuously through the bypass circuit and propofol 3 mg kg^{-1} was administered continuously intravenously. Anaesthetic agents were discontinued after the patients were haemodynamically stable on the intensive care unit (after T3). Postoperative sedation consisted of propofol 2 mg kg^{-1} in the propofol group and midazolam (2–4 mg boluses, with a cumulative dose ranging between 4 and 10 over the first 6 h after the surgery) in the volatile-anaesthetic groups.

All values are expressed as mean and standard deviation. Jugular venous saturation (Sj_{O_2}) data were compared using analysis of variance (ANOVA) factorial or repeated measures as appropriate. A P value of <0.05 was considered significant. When significance was found, post-hoc tests (Bonferoni/Dunn) with correction for multiple comparisons were applied.

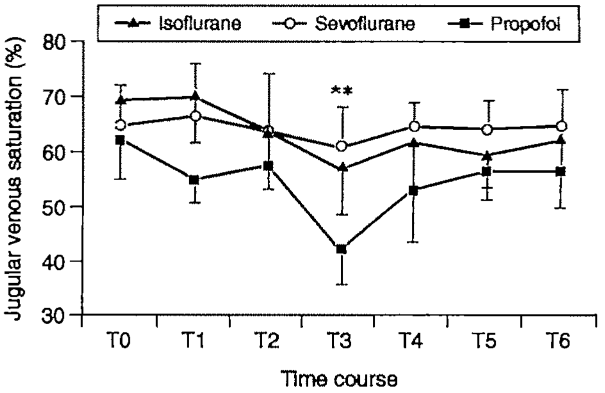

Fig 1 Time course of jugular venous saturation (Sj_{O_2}) values during the entire study period T0=after induction of anaesthesia, T1=30 min after starting cardiopulmonary bypass (CPB), T2=immediately after CPB; T3, T4. T5, T6=1, 6, 12, 18 after CPB. $^{**}P<0.05$ compared the propofol group with the isoflurane and sevoflurane groups

There were no significant differences between between the groups in age, height, weight, total CPB or aortic clamp time. Sj_{O_2} values were significantly lower than baseline 1 h after CPB in the propofol but not the isoflurane or the sevoflurane groups. Furthermore, Sj_{O_2} values were significantly higher during CPB in the isoflurane group ($P=0.0081$) and significantly lower 6 h after CPB in the sevoflurane group ($P=0.0447$) when compared to the propofol group (Fig. 1). MAP was maintained >50 mm Hg in all patients without significant differences between the three anaesthetic subgroups at any stage of the study.

Comment

We have demonstrated a significant decrease in Sj_{O_2} values 1 h after normothermic CPB during propofol but not isoflurane or sevoflurane anaesthesia for CPB surgery. Furthermore, Sj_{O_2} values are lower during propofol than isoflurane anaesthesia during CPB, and than sevoflurane anaesthesia 6 h after CPB.

Jugular venous desaturation has been reported to occur during and after CPB.[1-3] While the most prominent reductions in Sj_{O_2} occur during rewarming, such desaturation has also been reported early during the establishment of normothermic CPB.[2] Furthermore, a recent publication documented late jugular venous desaturation following hypothermic CPB.[4] The last two studies suggest that rewarming from hypothermic CPB cannot be the only cause of jugular desaturation, and that imbalances between cerebral oxygen supply and demand can occur in other settings associated with CPB. Our data suggest the occurrence of pathophysiological events in the first hour after CPB that are of a magnitude sufficient to disrupt normal flow-metabolism relationships.

Previous attempts to attenuate the early desaturation after CPB by reducing oxygen demand have been unsuccessful. Souter and colleagues used burst suppression doses of propofol as an adjunct in patients anaesthesized with isoflurane in an attempt to decrease cerebral oxygen requirement during weaning from CPB, but found no benefit.[5] Indeed their data show a trend for greater jugular desaturation in the group treated with propofol, which they attributed to an increased incidence of hypotension in this group. The reductions in Sj_{O_2} that we observed appear to be independent of changes in MAP, since there was no incidence of significant hypotension during the study period. Our data suggest that volatile anaesthesia can substantially attenuate jugular venous desaturation occurring during the entire study period when compared to patients receiving propofol anaesthesia. We do not have any data that provide an explanation for either the decrease in Sj_{O_2} or the difference that we have observed between the different anaesthetic/sedative regimens that were used in this study.

A disadvantage of this study protocol is the absence of continuous jugular saturation monitoring. The use of fibreoptic catheters might have allowed us to provide a more complete picture of cerebral blood flow adequacy during the study period. However, we had technical difficulties with continuous fibreoptic Sj_{O_2} monitoring during CPB, and our decision not to use this form of monitoring is supported by a recent paper that demonstrates problems with its use in the setting of CPB.[6]

While our continuing studies address both this issue and the mechanisms involved, our present results clearly show that the choice of anaesthetic agent may have important influences on cerebral oxygenation in some periods following CPB and provide a basis for further studies.

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Reference

1 Nakajima T, Kuro M, Hayashi Y, *et al* Clinical evaluation of cerebral oxygen balance during cardiopulmonary bypass: on-line continuous monitoring of jugular venous oxyhemoglobin saturation. *Anesth Analg* 1992; **74**: 630–5

2 Cook DJ, Oliver WC, Orszulak A, Daly RC. A prospective, randomized comparison of cerebral venous oxygen saturation during normothermic and hypothermic cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1994; **107**: 1020–9

3 Croughwell ND, Newman MF, Blumenthal JA, *et al.* Jugular bulb saturation and cognitive dysfunction after cardiopulmonary bypass. *Ann Thorac Surg* 1994; **58**: 1702–8

4 Souter MJ, Andrews PJD, Alston RP. Jugular venous saturation following cardiac surgery. *Br J Anaesth* 1998: **81**: 239–41

5 Souter MJ, Andrews PJD, Alston RP Propofol does not ameliorate cerebral venous oxyhemoglobin desaturation during hypothermic cardiopulmonary bypass. *Anesth Analg* 1998; **86**: 926–31

6 Millar SA, Alston RP, Souter MJ, Andrews PJD. Continuous monitoring of jugular bulb oxyhaemoglobin saturation using the ESLAB dual lumen oximetry catheter during and after cardiac surgery. *Br J Anaesth* 1999; **82**: 521–4

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Effect of anaesthesia on the cardiac response to intravenous adenosine†

N. J. Morgan-Hughes and K. M. Sherry*

Department of Anaesthesia, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK
**Corresponding author*

The cardiac response to intravenous adenosine 112 $\mu g\ kg^{-1}$ was studied in 16 patients scheduled for coronary artery bypass surgery before and during anaesthesia with 1% end-tidal isoflurane and fentanyl 10 $\mu g\ kg^{-1}$. Mean time from injection to onset of adenosine-induced PR prolongation was significantly greater during anaesthesia (12.8 (SD 5) *vs* 9.9 (3) s, P=0.032). Atrioventricular block (assessed by the total number of non-conducted P waves) was significantly less during anaesthesia (12 *vs* 27, P=0.016). We conclude that anaesthesia including 1% isoflurane and fentanyl 10 $\mu g\ kg^{-1}$ delays the onset and reduces the magnitude of adenosine-induced atrioventricular block.

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The therapeutic indication for intravenous adenosine is the conversion of paroxysmal supraventricular tachycardia. An intravenous dose of adenosine to awake subjects during sinus rhythm prolongs the PR interval, and can lead to complete atrioventricular block starting 10–20 s after injection and lasting less than 10 s.[1] Sinus bradycardia is also seen and occurs with onset and duration similar to the

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PR effect. These changes are followed by reflex sinus tachycardia.

Adenosine is a recommended first-line treatment for paroxysmal tachycardia occurring during anaesthesia.[2] No controlled studies have been carried out to assess if current dosage recommendations are appropriate in anaesthetized patients. The aim of this study was to assess the effect of anaesthesia on the cardiac response to adenosine.

Methods and results

After Local Ethics Committee approval and informed written consent had been obtained, 19 patients scheduled for elective coronary bypass surgery were recruited. Exclusion criteria comprised digoxin, theophylline or dipyridamole treatment, ECG conduction abnormalities, cardiac arrhythmia, left ventricular ejection fraction less than 50%, left main stem coronary disease and valvular heart disease requiring surgery. Anti-anginal medication was continued and patients were premedicated with intramuscular morphine 10 mg and metoclopramide 10 mg. Under local anaesthesia, cannulae were placed in an internal jugular vein (using a triple lumen catheter), a peripheral vein and a radial artery. Central venous, arterial pressure and ECG leads II and V5, including ST segment changes, were monitored continuously (Datex AS3, Engstrom, Helsinki, Finland). A three-lead ECG running at a paper speed of 100 mm s^{-1} (Mingocard 4, Siemens-Elma, Sweden) was used to record and later measure the PR and PP intervals. The study plan was based on one used previously to evaluate the clinical efficacy of adenosine in cardiac transplant patients.[3] Before anaesthesia, adenosine 112 $\mu g\ kg^{-1}$ was injected rapidly via the distal lumen of the jugular venous catheter and flushed with 10 ml saline. A continuous ECG was recorded from 30 s before to 2 min after injection. Anaesthesia was induced using etomidate 10 mg and fentanyl 10 $\mu g\ kg^{-1}$. Pancuronium 0.1 mg kg^{-1} was used to facilitate tracheal intubation and ventilation of the lungs with oxygen in air to an end-tidal carbon dioxide concentration of 4–4.5%. Anaesthesia was maintained using isoflurane. Metaraminol 0.25–0.5 mg was used if needed to maintain the systolic blood pressure at or above 90 mm Hg. When a stable end-tidal isoflurane concentration of 1% had been established, the sequence of ECG recording and adenosine administration was repeated.

PR and PP intervals before and during anaesthesia were measured to within 5 ms and plotted. Baseline intervals were measured from the mean of five beats before adenosine injection and noted together with baseline mean arterial pressure.

Time to onset of the PR effect was defined as the time from completion of adenosine injection to the start of PR prolongation, as estimated from the plot of PR intervals. The number of non-conducted P waves after adenosine injection was used as a measure of the magnitude of the effect on atrioventricular conduction. Duration of the PR effect was taken as the time during which the PR interval was increased by 10 ms or more compared with baseline.

Sinus bradycardia after adenosine injection was an inconsistent finding. Therefore, no attempt was made to evaluate bradycardia from the magnitude or duration of PP prolongation. In addition, some patients had atrial ectopic beats or transient sinus bradycardia early after adenosine injection. This may have been a topical effect of adenosine on the sinus node from within the right atrium.

The reflex sinus tachycardia that followed the direct cardiac effect of adenosine was quantified from each recording as the minimum PP interval observed after drug administration, and was expressed as a percentage of the baseline PP interval.

Data analysis was performed using Microsoft Excel version 5c. Paired *t* tests were used to analyse continuous variables before and during anaesthesia. The total number of non-conducted P waves before and during anaesthesia was compared using the chi-squared test. Statistical significance was defined as $P<0.05$.

Three of the 19 patients recruited to the study developed a nodal rhythm after induction of anaesthesia and were excluded from the analysis. Sixteen patients (12 male) with a mean age of 57 (SD 10) years and mean weight of 84 (16) kg completed the study. The results are given in Table 1.

Comment

Our study population was selected for its routine invasive monitoring. This choice can be criticized. Many anti-anginal drugs have cardiac electrophysiological effects, but these drugs were continued as withdrawal could have increased the risk of perioperative myocardial ischaemia. Similarly, we thought it unethical to omit premedication and the 'awake' studies were performed in premedicated patients. In addition these patients had coronary disease, which could reduce drug delivery to the cardiac conduction system. We believe these criticisms are partly offset by the paired nature of the study; each patient was acting as their own control. A criticism of the study design is that effects of adenosine observed during sinus rhythm are surrogate end-points for the drug's clinical effect, which is to end an attack of tachycardia. However, similar surrogate end-points have been used previously.[3]

We showed that anaesthesia with 1% end-tidal concentration isoflurane/fentanyl increases the time to onset and reduces the magnitude of adenosine-induced atrioventricular nodal block. A longer transit time from the point of injection to the coronary circulation during anaesthesia could explain the delay in onset of the effect of adenosine, and the reduced effect of adenosine because of the drug's very short plasma half-life (less than 2 s).[4] A longer transit time would allow greater adenosine metabolism and reduce the drug concentration reaching the effector site.

Anaesthesia attenuated the reflex tachycardia and, by inference, the reflex sympathetic activation[5] that follows

Table 1 Baseline ECG measurements, baseline mean arterial pressure and cardiac response to intravenous adenosine 112 $\mu g\ kg^{-1}$ before and during 1% isoflurane anaesthesia Values are mean (SD) *Two patients did not develop adenosine-induced PR prolongation while awake, and these two patients, together with a third, did not develop it during anaesthesia Paired *t* tests were therefore performed only on data from the 13 patients with PR prolongation both before and during anaesthesia

	Before anaesthesia	During anaesthesia	*P* value
Baseline PR interval (ms)	177 (25)	166 (24)	0.007
Baseline PP interval (ms)	1067 (168)	1099 (253)	0.546
Baseline mean arterial pressure (mm Hg)	88 (11)	76 (9)	0.003
Time to onset of PR prolongation in 13 patients (s)*	9.9 (3)	12.8 (5)	0.032
Duration of PR prolongation in 13 patients (s)*	10.1 (3)	10.1 (4)	0.595
Total number of non-conducted P waves	27	12	0.016
Minimum PP interval after adenosine (% of baseline)	75 (8)	87 (6)	0.001

the direct cardiac effects of an intravenous bolus of adenosine. This could reflect anaesthesia-induced sympatholysis.

The attenuation of the atrioventricular blocking effect of adenosine shown in this study is a consideration when an anaesthetized patient develops supraventricular tachycardia. A standard intravenous adenosine 3, 6, 12 mg regimen without additional higher doses is currently recommended. We suggest that, for the anaesthetized patient, the current maximum dose presented above needs to be reviewed.

References

1 DiMarco JP, Sellers TD, Berne RM, West GA, Belardinelli L. Adenosine: electrophysiologic effects and therapeutic use for terminating paroxysmal supraventricular tachycardia. *Circulation* 1983, **68**: 1254–63

2 Hillel Z, Thys DM. Electrocardiography. In: Miller RD, ed *Anesthesia*. New York: Churchill Livingstone, 1994, 1241

3 Ellenbogen KA, Thames MD, DiMarco JP, Sheehan H, Lerman BB. Electrophysiological effects of adenosine in the transplanted human heart. evidence of supersensitivity *Circulation* 1990, **81**: 821–8

4 Moser GH, Schrader J, Deussen A. Turnover of adenosine in plasma of human and dog blood. *Am J Physiol* 1989, 256· C799–806

5 Biaggioni I, Killian T, Mosquedo-Garcia R, Robertson RM, Robertson D. Adenosine increases sympathetic nerve traffic in humans. *Circulation* 1991; **83**: 1668–75

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Carbon dioxide elimination during high-frequency jet ventilation for rigid bronchoscopy

P. Biro[1]*, M. Layer[2], K. Wiedemann[2], B. Seifert[3] and D. R. Spahn[1]

[1]Institute of Anaesthesiology, University Hospital Zurich, Raemistrasse 100, CH-8091 Zurich, Switzerland,
[2]Department of Anaesthesiology, Thoraxklinik, Amalienstrasse 5, D-69126 Heidelberg, Germany and
[3]Department of Biostatistics, University of Zurich, CH-8006 Zurich, Switzerland
**Corresponding author*

Oxygen saturation and carbon dioxide values should be monitored during high-frequency jet ventilation (HFJV). Modern transcutaneous $P\text{CO}_2$ (Ptc_{CO_2}) measurement allows the estimation of ventilation efficiency. We studied how tests of lung function could predict carbon dioxide elimination during HFJV. Lung function tests from 180 adult patients undergoing rigid bronchoscopy were analysed as factors affecting carbon dioxide elimination. The lung function test results showed a significant relationship with the efficiency of carbon dioxide elimination; the greatest impairment of carbon dioxide elimination was found in patients with combined abnormalities of lung function. Further factors associated with difficult carbon dioxide elimination were male gender and elevated body weight. Of the patients investigated, 72% had normal carbon dioxide elimination, whereas in 23% hypercapnia could be avoided only by increasing the driving pressure. The prevalence of abnormal preoperative lung function test results predicts (sensitivity 76%, positive predictive value 27%) impaired carbon dioxide elimination during jet ventilation and rigid bronchoscopy.

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High-frequency jet ventilation (HFJV) is a convenient method of ventilation during rigid bronchoscopy, since it offers optimal visibility and easy access for diagnostic and surgical instruments into the airway. However, monitoring of gas exchange is more difficult than during conventional ventilation and requires special equipment. We have recently described a new transcutaneous blood gas sensor prototype, the Sp_{O_2}-Ptc_{CO_2} ear probe (Linde Medical Instruments, Basel, Switzerland). This device provides reliable carbon dioxide partial pressure values compared with simultaneously determined Pa_{CO_2}, and has an *in vivo* latency period of 57±20 s.[1] Because of the speed and ease of use of this device, we now routinely use transcutaneous carbon dioxide measurement during HFJV as an approximation for Pa_{CO_2}. Since the jet driving pressure (DP) and the resulting transcutaneous $P\text{CO}_2$ (Ptc_{CO_2}) values are inversely related, we calculate a carbon dioxide elimination coefficient (Ec_{CO_2}) which helps to quantify the individual carbon dioxide elimination capacity under HFJV and under standardized conditions.[2]

A value of 1.0 results if Ptc_{CO_2} is normal (37.5 mm Hg) during jet ventilation with a moderate DP of 2.0 atm and represents a normal carbon dioxide elimination capacity. Reduced values indicate impaired carbon dioxide elimination. As an empirical cut-off value, we use an Ec_{CO_2} of 0.75 to differentiate between normal and compromised carbon dioxide elimination. We set out to assess the relation between preoperative lung function test results and carbon dioxide elimination during jet ventilation for rigid bronchoscopy.

Methods and results

After informed consent had been obtained, 180 adult patients of ASA physical status 1–4 who were scheduled for elective interventional rigid bronchoscopy under general anaesthesia and HFJV were included in this study. Vital capacity (VC) and forced expiratory volume in 1 s (FEV_1) were measured and compared with values predicted from standard equations.[3] A restrictive pattern was assumed if the measured VC was below 70% of the predicted value, and an obstructive abnormality if the measured FEV_1 was below 70% of the predicted value.

Total intravenous anaesthesia (TIVA) was conducted with propofol and remifentanil for induction and maintenance and succinylcholine for muscle relaxation. In addition to usual monitoring, continuous transcutaneous blood gas measurement with a calibrated Sp_{O_2}-Ptc_{CO_2} ear-clip sensor prototype (Linde Medical Instruments, Basel, Switzerland) was used.[1] Jet ventilation was performed with an AMS 1000 Universal Jet Ventilator- (Acutronic Medical Systems, Hirzel, Switzerland) via the rigid bronchoscope. A respiratory frequency of 150 cycles min^{-1} and an inspiration duration of 40% were set during the study. Therefore, the DP was the only variable in the HFJV setting.

The DP was set at 1.5, 2.0 and 2.5 atm for 5 min each, and the resulting Ptc_{CO_2} was documented 3 min after each change of DP setting. If oxygenation was poor (Sp_{O_2} <89%), HFJV was supplemented by manually assisted ventilation. Ec_{CO_2} values calculated at various DP settings were averaged. The physical and clinical characteristics of patients with normal carbon dioxide elimination were compared with those of patients with impaired elimination by the use of the Mann–Whitney test. The influence of lung function on Ec_{CO_2} was tested for dissimilarity by one-way analysis of variance (ANOVA). *Post hoc* comparisons of categories were performed using the Bonferroni–Dunn test. Frequencies were examined for variability by the chi-squared test; $P < 0.05$ was considered significant. In eight patients the Sp_{O_2} could not be maintained continuously above 89%, which prevented further analysis of carbon dioxide elimination under standardized study conditions. Thus, the data come from 172 patients. Ptc_{CO_2} values had a range of 24.8–66.8 mm Hg. One hundred and thirty-five patients had normal carbon dioxide elimination ($Ec_{CO_2} >$ 0.75), and in 37 patients carbon dioxide elimination was compromised ($Ec_{CO_2} <$ 0.75). Patients with compromised carbon dioxide elimination had a significantly greater body weight and a smaller VC and FEV_1, and the percentage of males was higher in this group of patients (Table 1).

Allocation of patients to the four prospectively defined patients the Sp_{O_2} could not be maintained continuously with normal lung function, (ii) 57 patients (33%) with obstructive abnormality, (iii) 22 patients (13%) with restrictive abnormality and (iv) 24 patients (14%) with combined (obstructive plus restrictive) abnormality. Elimination of carbon dioxide, as assessed by Ec_{CO_2}, was best in patients with normal lung function (P = 0.0007 in the overall ANOVA) and deteriorated progressively in patients with obstructive, restrictive and combined abnormality.

Normal values of lung function variables (VC and/or FEV_1) had a negative predictive value of 87% for normal carbon dioxide elimination ($Ec_{CO_2} >$ 0.75), whereas the prevalence of at least one pathological lung function variable resulted in a positive predictive value of only 27% for compromised carbon dioxide elimination (Ec_{CO_2} < 0.75). Of patients with impaired carbon dioxide elimination ($Ec_{CO_2} <$ 0.75), 76% had abnormal lung function tests (sensitivity) and normal results were present in only 44% of patients with normal carbon dioxide elimination (Ec_{CO_2} > 0.75) (specificity).

Table 1 Biometrical and clinical data during jet ventilation for rigid bronchoscopy in patients with normal and compromised carbon dioxide elimination. Frequencies were compared with the chi-squared test, the other variables with the Mann–Whitney test). Values are mean (SD). n.s.' = not significant

	Normal CO_2 elimination ($Ec_{CO_2} > 0.75$)	Compromised CO_2 elimination ($Ec_{CO_2} < 0.75$)	Statistical significance
Patients (*n*)	135	37	
Males (*n*)	82 (63%)	29 (76%)	$P<0.05$
Age (years)	58 (17–31)	59 (83–78)	n.s
Height (cm)	171 (9)	171 (7)	n.s
Weight (kg)	72 (13)	79 (15)	$P<0.05$
Predicted VC (l)	3.81 (0.87)	3.79 (0.65)	n.s
Actual VC (l)	3.16 (0.96)	2.57 (0.93)	$P<0.05$
Predicted FEV_1 (l)	3.26 (0.77)	3.27 (0.55)	n.s
Actual FEV_1 (l)	2.22 (0.78)	1.73 (0.73)	$P<0.05$
$FEV_1 \times 100/VC$ (%)	70.4 (12.9)	67.8 (15.3)	n.s
Ventilation duration (min)	14 (11)	14 (7)	n.s
Mean Ptc_{CO_2} (mm Hg)	40.8 (6.9)	52.4 (6.1)	$P<0.01$
Mean DP (atm)	1.9 (0.3)	2.3 (0.3)	$P<0.01$
Mean Ec_{CO_2}	1.02 (0.18)	0.66 (0.08)	$P<0.01$
Lung function categories (*n*)			
Normal	60	9	$P=0.007$
Obstructive	48	8	
Restrictive	13	10	
Combined	14	10	

Comments

During HFJV the assessment of carbon dioxide status is a challenge. An arterial catheter may be not always indicated or feasible and capnography values may be invalid unless ventilation is interrupted regularly or special equipment is used. Recently introduced transcutaneous P_{CO_2} monitoring allows non-invasive and continuous carbon dioxide surveillance with a fair degree of precision and an acceptable response time.

The definition of a tolerable upper limit for Ptc_{CO_2} may be arbitrary; however, in the vast majority of patients, 50 mm Hg can be tolerated safely for the duration of a bronchoscopic intervention. Although in some cases even higher carbon dioxide values may be acceptable,[4] Ptc_{CO_2} values between 30 and 50 mm Hg are a reasonable routine target. If a Ptc_{CO_2} value of 50 mm Hg is an acceptable maximum while ventilating with a moderate DP of 2.0 atm, the resulting Ec_{CO_2} must be above 0.75. Therefore, we used this as a cut-off value to divide the patients into two categories: 'normal' and 'compromised' carbon dioxide elimination.

The physical and clinical data show relevant differences between the two defined carbon dioxide elimination groups (Table 1). Male gender and high body weight are known to be associated with difficulty in achieving adequate gas exchange during HFJV, particularly with carbon dioxide elimination.[2 5 6] The same is true for abnormal lung function, but this depends on the type and degree of the abnormality. Surprisingly, obstructive lung disease, which is usually considered an important hindrance to carbon dioxide elimination during jet ventilation,[7 8] was less relevant than restrictive lung function. However, the preoperative abnormal lung function predicts difficult carbon dioxide elimination (sensitivity 76%) but normal results are not good predictors of normal carbon dioxide elimination during jet ventilation (specificity 44%).

In summary, most patients with abnormal pulmonary function tests undergoing rigid bronchoscopy (96%) can be ventilated adequately with HFJV. Measurement of lung function variables such as VC and FEV_1 and the prevalence of other cofactors, such as male gender and elevated body weight, can help to estimate the expected carbon dioxide elimination. Patients with normal carbon dioxide elimination will require a lower DP. This has the benefits of lowering airway pressure to the necessary minimum and reducing the adverse effects of HFJV, such as cooling and drying of the tracheobronchial epithelium.

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References

1 Rohling R, Biro P. Clinical investigation of a new combined pulse oximetry and carbon dioxide tension sensor in adult anaesthesia. *J Clin Monit* 1999; **15**: 23–7

2 Biro P, Eyrich G, Rohling R. The efficiency of CO_2 elimination during high-frequency jet ventilation for laryngeal microsurgery. *Anesth Analg* 1998; **87**: 180–4

3 Lollgen H. *Kardiopulmonale Funktionsdiagnostik*. Wehr/Baden: Ciba-Geigy, 1995

4 Stock C. Carbon dioxide and apnea: common knowledge and common sense. *J Clin Anesth* 1998; **10**. 181–3

5 Ayuso MA, Luis M, Sala X, Martinez G, Sanchez J, Alarcon A. Comparative study of high-frequency jet ventilation in 4 types of patients undergoing laryngeal microsurgery. *Rev Esp Anestesiol Reanim* 1997; **44**: 7–12

6 Lichtwarck-Aschoff M, Zimmermann GJ, Erhardt W. Reduced CO_2-elimination during combined high-frequency ventilation compared to conventional pressure-controlled ventilation in surfactant-deficient piglets. *Acta Anaesthesiol Scand* 1998; **42**: 335–42

7 Rouby JJ, Simonneau G, Benhamou D, et *al*. Factors influencing pulmonary volumes and CO_2 elimination during high-frequency jet ventilation. *Anesthesiology* 1985; **63**: 473–82

8 Bourgain J-L, McGee K, Cosset MF, Bromley L, Meistelman C. Carbon dioxide monitoring during high frequency jet ventilation for direct laryngosopy. *Br J Anaesth* 1990; **64**: 327–30

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Cp50 of propofol with and without nitrous oxide 67%

P. C. Stuart[1 2], S. M. Stott[2], A. Millar[1], G. N. C. Kenny[1] and D. Russell[1 2]*

[1]Department of Anaesthesia, University of Glasgow, Glasgow G31 2ER, UK. [2]Department of Anaesthesia, Southern General Hospital, 1345 Govan Road, Glasgow G51 4TF, UK

**Corresponding author*

The target concentration of propofol required to prevent response to surgical incision was determined in 60 unpremedicated ASA I or II patients, who breathed either oxygen-enriched air or nitrous oxide 67% in oxygen. Propofol was infused using a target-controlled infusion system incorporating the standard 'Diprifusor' pharmacokinetic model, with the target concentration for each patient decided by up/down sequential allocation. Presence or absence of movement in response to a groin incision was determined by the surgeon. The calculated blood concentration at which 50% of patients responded ($Cp50_{calc}$), determined by probit analysis, was 6.8 μg ml^{-1} for patients who breathed oxygen-enriched air and 4.9 μg ml^{-1} for those who breathed nitrous oxide 67% in oxygen.

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Target-controlled infusion systems for propofol allow anaesthetists to titrate target blood propofol concentration according to requirement, in the same way that inspired concentrations of inhalational anaesthetic agents are adjusted according to response. Eger, Saidman and Brandstater[1] determined the minimum alveolar concentration (MAC), that is, the alveolar concentration of an inhalational agent at which 50% of subjects fail to respond to a standard surgical stimulus, for a series of inhalational agents, initially in anaesthetized dogs. This has become the standard experimental technique for defining the potency of inhalational anaesthetic agents and provides important guidelines for drug administration.

Davidson and colleagues[2] determined the $Cp50_{calc}$ for propofol in patients premedicated with temazepam. $Cp50_{calc}$ is defined as the calculated plasma concentration at which 50% of patients anaesthetized with an intravenous agent do not respond to a standard surgical stimulus, the calculated plasma concentration having been maintained for long enough to permit equilibration with the effect site.[3] Anaesthesia was induced and maintained with propofol by target-controlled infusion; after an equilibration period of ≥12 min a standard surgical incision was made. Cp50 for the calculated propofol concentration was 6.0 μg ml^{-1} in patients breathing oxygen-enriched air and 4.5 μg ml^{-1} in those breathing nitrous oxide 67% in oxygen. Since pharmacological premedication is not always appropriate, we considered it essential to determine the Cp50 for propofol in unpremedicated patients. This is particularly relevant to modern daycase anaesthetic practice.

Methods and results

Sixty unpremedicated patients (ASA I and II, aged 16–70 yr) scheduled for inguinal hernia repair or sapheno-femoral ligation were studied, with written informed consent and Institutional Ethics Committee approval. Exclusion criteria were concurrent medication with analgesics, and obesity (body mass index ≥35 kg m^{-2}). Anaesthesia was induced and maintained with propofol, using a target-controlled infusion system which incorporated the standard 'Diprifusor' pharmacokinetic model proposed by Gepts and colleagues,[4] and later modified by Marsh and colleagues.[5] Patients were randomized to breathe either oxygen-enriched air or nitrous oxide 67% in oxygen from a tightly fitting facemask. The target concentration for the first patient in each group was 0.5 μg ml^{-1} higher than the Cp50 values determined by Davidson and colleagues.[2] After they had lost consciousness, patients were prepared for surgery but were otherwise left as unstimulated as possible.

A minimum of 12 min after induction (to allow equilibration between blood and brain propofol concentrations, and inspired/expired nitrous oxide partial pressures), a groin incision was made. The surgeon, who was blinded to the target propofol concentration in use and to whether the patient was breathing oxygen-enriched air or nitrous oxide

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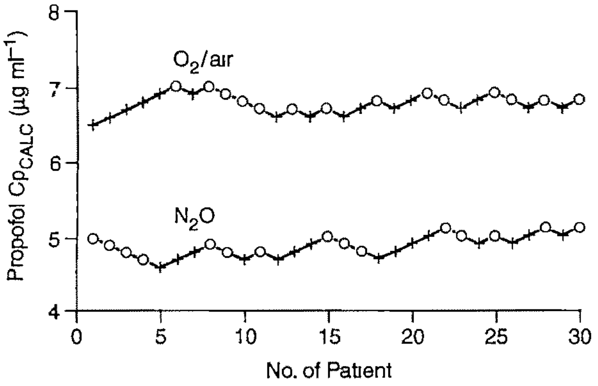

Fig 1 Dose–response data for each of the patients breathing either oxygen-enriched air or nitrous oxide 67% in oxygen; movement (+) and lack of movement (O) in response to incision

in oxygen, decided if there was any 'gross purposeful movement'. This definition of movement was the same as that used by Eger, Saidman and Brandstater in their MAC studies.[1] Subsequent patients in each group had anaesthesia induced to a target concentration 0.1 µg ml^{-1} higher or lower than before, using up/down sequential allocation; if the patient moved on incision, the target propofol concentration for the next patient in that group was set to 0.1 µg ml^{-1} higher than before. If no movement was detected, the target for the next patient was 0.1 µg ml^{-1} lower than the previous patient in that group. The collection of study data was complete when the response to surgical incision was noted, and thereafter an appropriate dose of opioid (fentanyl or alfentanil) was administered to deepen anaesthesia. Probit analysis[6] was used to assess the dose–response data, with Minitab version 12 for Windows 95.

Mean (range) age and mean (SD) weight were 49.6 (18–70) yr and 71.1 (11.4) kg, respectively, in the nitrous oxide group and 41.2 (18–68) yr and 73.7 (15.6) kg, respectively, in those breathing oxygen-enriched air. The gender ratio (male:female) was 16:14 in the nitrous oxide group, and 19:11 in those breathing oxygen-enriched air. Arterial pressure was measured non-invasively every 3 min. Patients remained haemodynamically stable (within 20% of preoperative mean arterial pressure). No patients required assistance with ventilation (Sp_{O_2} remained >94% and FE'_{CO_2} was <7.5 kPa) and on direct questioning at the postoperative visit no patient had recall of any event during anaesthesia or surgery. The target blood propofol concentration for each patient and the response to incision are shown in Fig. 1.

The Cp50 for the target propofol concentration, corrected to one decimal place (95% confidence intervals), was 4.9 (4.8–5.0) µg ml^{-1} in patients breathing nitrous oxide 67% and 6.8 (6.7–6.9) µg ml^{-1} in those breathing oxygen-enriched air.

Comment

The Cp50 values that we have determined are slightly higher than those described by Davidson and colleagues in their premedicated patients.[2] We found that the administration of nitrous oxide 67% in oxygen reduces propofol Cp50 by 28%, which is similar to the 25% reduction demonstrated previously.[2]

Cp95 (the concentration at which only 5% of patients respond to incision) might be considered more clinically relevant than Cp50. Up/down sequential allocation and probit analysis are designed to determine Cp50 and, while it is possible to estimate Cp95 by extrapolation of the 'best-fit' line on probit graphs, the confidence intervals are so large that it is impossible to draw any firm conclusions from the result. In our study, propofol $Cp95_{calc}$ (95% confidence intervals) was 5.3 (5.1–18.9) µg ml^{-1} for patients who breathed nitrous oxide 67%, and 7.1 (6.9–9.5) µg ml^{-1} for those who breathed oxygen-enriched air.

We conclude that, in unpremedicated patients, if anaesthesia is induced to a target propofol concentration of 6.8 µg ml^{-1}, or 4.9 µg ml^{-1} when nitrous oxide 67% is used, there is a 50% chance that patients will move in response to a skin incision made a l≥12 min later.

References

1 Eger EI, Saidman LJ, Brandstater B. Minimum alveolar anaesthetic concentration: a standard anaesthetic potency *Anesthesiology* 1965; **26**: 756–63

2 Davidson JAH, MacLeod AD, Howie JC, White M, Kenny GNC. Effective concentration 50 for propofol with and without 67% nitrous oxide. *Acta Anaesthesiol Scand* 1993; **37**: 458–64

3 Glass PSA, Glen JB, Kenny GNC, Schuttler J, Shafer SL Nomenclature for computer-assisted infusion devices. *Anesthesiology* 1997; **86**: 1430

4 Gepts E, Camu F, Cockshott ID, Douglas EJ Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesth Analg* 1987; **66**. 1256–63

5 Marsh B, White M, Morton N, Kenny GNC Pharmacokinetic model driven infusion of propofol in children *Br J Anaesth* 1991, **67**: 41–8

6 Kenakin TP. *Pharmacologic Analysis of Drug–Receptor Interaction*, 2nd edn New York: Raven Press, 1993

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BJA

CASE REPORTS

Anticoagulant-induced pseudothrombocytopenia in a patient presenting for coronary artery bypass grafting

N. J. Wilkes*, N. A. Smith and S. V. Mallett

Department of Anaesthesia, Royal Free Hampstead NHS Trust, Pond Street, London NW3 2QG, UK

**Corresponding author*

A 73-yr-old man with severe ischaemic heart disease presented for coronary artery bypass grafting. His preoperative platelet count, obtained from an ethylene diamine tetraacetic acid (EDTA) sampling bottle, was 61×10^9 litre^{-1}, but he had no history of bleeding problems. Previous platelet counts demonstrated results ranging from 16×10^9 litre^{-1} to 254×10^9 litre^{-1} with variable degrees of *in vitro* platelet clumping. Preoperative thrombelastography reflected a normal coagulation profile. The laboratory findings and the absence of a history of haemorrhagic complications suggested a diagnosis of EDTA-dependent pseudothrombocytopenia. We present the perioperative implications of this *in vitro* phenomenon and methods of detecting the functional and numerical integrity of circulating platelets.

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Pre- and postoperative thrombocytopenia are factors predictive of increased haemorrhage and increased blood transfusion requirements after cardiac surgery.[1 2] Functional impairment of platelets resulting from cardiopulmonary bypass further compromises haemostatic mechanisms.[3] Re-exploration for haemorrhage after coronary artery bypass grafting is associated with increased length of hospital stay and increased mortality.[4] Thrombocytopenia is undesirable and may result in the need for platelet transfusion.

Pseudothrombocytopenia is a rare finding caused by *in vitro* aggregation of platelets in sampling bottles containing ethylene diamine tetraacetic acid (EDTA) as an anticoagulant.[5] Bartels and colleagues demonstrated a prevalence of 0.1% in a general hospital population.[6] Silvestri and co-workers discovered that 15% of patients referred to a specialist unit with isolated thrombocytopenia were, in fact, cases of EDTA-dependent pseudothrombocytopenia.[7] The phenomenon is thought to be the result of an altered conformation of platelet membrane glycoproteins or anionic phospholipids after exposure to EDTA and cold temperature, leading to the binding of various immunoglobulins of the IgG, IgM or IgA class, which then promote platelet aggregation.[8] In some patients, antibodies against the IIb fraction of the platelet membrane glycoprotein GP IIb/IIIa complex have been discovered.[9 10] This structure becomes exposed as a result of the chelating effect of EDTA on calcium ions. Incubation of the blood sample with sodium citrate instead of EDTA usually prevents the process and can be considered diagnostic of EDTA-dependent pseudothrombocytopenia.

Misinterpretation of an artificially low platelet count may lead to the unnecessary transfusion of platelets, increasing the risk of associated morbidity. In the absence of a reliable platelet count, assessment of platelet function may be difficult. Testing for bleeding time has been shown to be a poor predictor of haemorrhage associated with surgical procedures.[11] Thrombelastography, on the other hand, reflects platelet function and predicts postoperative haemorrhage after cardiac surgery.[12]

Case report

A 73-yr-old man with triple-vessel coronary disease presented for coronary artery bypass grafting. His past medical history comprised ischaemic heart disease with two prior myocardial infarctions and unstable angina pectoris; congestive cardiac failure; chronic obstructive airways disease; and cerebrovascular disease with several transient ischaemic attacks and a prior cerebrovascular accident. He denied any history of bleeding problems. His current medications were beclomethasone and salbutamol inhalers, nifedipine, amiloride, furosemide and glyceryl trinitrate spray as required. He had stopped smoking recently. On chest

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Table 1 Perioperative laboratory findings and TEG results. For platelet counts we used sampling bottles containing EDTA or sodium citrate (citrate). For preoperative TEG samples, we used native cups (n), intraoperative samples were incubated in heparinase-coated cups (hp), and for postoperative samples both techniques were used. APTT = activated partial thromboplastin time, R time = reaction time, K time = clot formation time; alpha angle = rate of clot growth, NA = not applicable. Reference ranges: haemoglobin, 13.5–17.5 g dl^{-1}, platelets, 140×10^9 to 400×10^9 $litre^{-1}$, prothrombin time, 12–16 s, APTT, 28–38 s, fibrinogen, 1.5–4.0 g $litre^{-1}$; R time, 40.0±6.5 mm, K time, 16.0±5.0 mm, α angle, 29.0±7.5°, maximum amplitude, 50.0±5.0 mm

	Preoperative	Intraoperative	Postoperative
Platelet count ($\times10^9$ $litre^{-1}$)	61 (EDTA)/68 (citrate)	39 (EDTA)	33 (EDTA)/60 (citrate)
Haemoglobin (g dl^{-1})	12.2	8.4	9.4
Prothrombin time (s)	14.2	NA	19.8
APTT (s)	35.4	NA	55.5
Fibrinogen (g $litre^{-1}$)	2.5	NA	1.6
ACT (s)	130	760	129
R time (mm)	36.5 (n)	15.5 (hp)	38.5/35.5 (n/hp)
K time (mm)	11.5 (n)	7.5 (hp)	19.0/14.5 (n/hp)
Alpha angle (degrees)	36.0 (n)	45.0 (hp)	21.0/23.0 (n/hp)
Maximum amplitude (mm)	55.5 (n)	70.0 (hp)	43.5/62.5 (n/hp)

examination, end-expiratory wheezes were audible in all areas. No petechiae were seen and splenomegaly was not detected. His preoperative full blood count and coagulation profile were within normal limits, except for a low platelet count of 61×10^9 $litre^{-1}$, obtained from an EDTA sampling bottle. Careful investigation of previous platelet counts revealed results ranging from 16×10^9 $litre^{-1}$ to 254×10^9 $litre^{-1}$ over a period of 6 yr. Platelet clumps had been noted in some of these samples and were invariably associated with low platelet concentrations, consistent with a diagnosis of pseudothrombocytopenia. A citrated blood sample (these are not usually associated with platelet clumping) was taken 3 days before operation and demonstrated a low platelet count of 68×10^9 $litre^{-1}$. A further recent sample, collected within an EDTA bottle, however, showed a normal platelet count of 254×10^9 $litre^{-1}$.

Because of the inconsistency of the findings, we decided to rely on thrombelastographic analysis (TEG) for our decision to proceed with the surgical procedure and for our intraoperative transfusion strategy. The preoperative TEG showed normal values (Table 1). The alpha-angle and the maximum amplitude, parameters denoting platelet function and platelet–fibrin interaction, were within the normal range. Findings were similar throughout the surgical procedure and into the postoperative period. Further perioperative platelet counts and the results of pre- and postoperative coagulation profiles were recorded (Table 1). After administration of heparin 24 000 iu, the activated coagulation time (ACT) rose from 130 to 760 s. Protamine reversal resulted in an ACT of 129 s. Postoperative chest tube drainage amounted to 520 ml in the first 24 h. Only one unit of blood was transfused postoperatively, keeping the haemoglobin above 8 g dl^{-1} in accordance with our established transfusion protocol. Two further concurrent blood samples were taken in the postoperative period, using EDTA and citrate respectively. The EDTA sample showed a platelet count of 33×10^9 $litre^{-1}$ and the citrated container a platelet count of 60×10^9 $litre^{-1}$. Both sampling bottles contained platelet clumps.

Discussion

Thrombocytopenia may be a result of impaired platelet production or accelerated platelet destruction (Table 2). In some cases, the underlying pathology cannot be identified. In 1996, the Task Force on Blood Component Therapy of the American Society of Anesthesiologists suggested that prophylactic platelet transfusion was rarely indicated in surgical patients with platelet counts greater than 100×10^9 $litre^{-1}$, and was usually indicated for platelet counts below 50×10^9 $litre^{-1}$. In patients with intermediate platelet counts (50×10^9 $litre^{-1}$ to 100×10^9 $litre^{-1}$), the risk of bleeding should be assessed and factors that adversely affect platelet function, such as the use of extracorporeal circulation, should be taken into account.[13] Doubts about the wisdom of administering platelet concentrates to our patient arose because of the enormous variation in past platelet counts, the presence of clumping and the absence of a clinical history, indicating a possible diagnosis of pseudothrombocytopenia. We were, however, intrigued by the inconsistency of the results and the absence of normal platelet counts with citrated containers, which have been recommended for use in patients with pseudothrombocytopenia to avoid platelet clumping.[6] A preoperative citrated sample showed thrombocytopenia with clumping, whereas an earlier sample containing EDTA demonstrated a normal platelet count. Both samples taken postoperatively, containing EDTA and citrate respectively, showed low platelet counts and clumps.

Table 2 Causes of thrombocytopenia

Impaired platelet production	
	Marrow infiltration (leukaemia, myelofibrosis)
	Myelosuppressive drugs (antimitotics, ethanol, thiazide diuretics)
	Infection (rubella, cytomegalovirus)
	Congenital amegakaryocytic thrombocytopenia
Accelerated platelet destruction	
	Idiopathic thrombocytic purpura
	Drug-induced thrombocytopenia (heparin, quinidine)
	Neonatal thrombocytopenia
	Disseminated intravascular coagulation
Sequestration of platelets	
	Splenomegaly
Pseudothrombocytopenia	

This inconsistency encouraged us to search the literature. Schrezenmeier and colleagues found that anticoagulation with not only EDTA but also sodium oxalate and sodium citrate induced platelet clumping *in vitro*.[14] Bizzaro reported that 20% of a large series of patients with pseudothrombocytopenia developed platelet clumping not only with EDTA but also with citrated samples.[15] His findings confirmed that *in vitro* platelet aggregation was a gradual process that was more likely to develop at room temperature than at body temperature. The author therefore recommended immediate analysis of blood samples at 37°C, although even at this temperature platelet clumping was noted in 20% of patients. These findings would explain the apparent inconsistencies in platelet counts in our patient. EDTA-containing samples with high platelet counts may have been analysed earlier and at a higher temperature than some of the citrated samples that showed low platelet counts. Undoubtedly, however, in our patient both EDTA and citrate had the capacity to induce pseudothrombocytopenia.

Dalamangas and Slaughter reported a patient with EDTA-dependent pseudothrombocytopenia presenting for coronary artery bypass grafting and aortic valve replacement.[16] Citrated blood samples showed a normal platelet count, facilitating accurate diagnosis. The more complex findings in our patient required additional tests to establish that *in vivo* platelet function was normal. Thrombelastography is a useful near-patient test of platelet function.[17] The MA shows significant correlation with the platelet count, and also with platelet binding to ADP and collagen, reflecting platelet activity. The alpha angle is reduced in thrombocytopenia, indicating a reduced rate of clot formation. Normal thrombelastographic findings reassured us that our patient presented with anticoagulant (EDTA and citrate)-induced pseudothrombocytopenia but had normal *in vivo* platelet function. An unnecessary platelet transfusion was avoided and we were satisfied that no abnormal postoperative haemorrhage was to be anticipated as a result of thrombocytopenia.

In summary, this case demonstrated that a low preoperative platelet count may, on rare occasions, be the result of a laboratory artefact. In patients presenting for surgery, a critical perspective is recommended if the absence of a clinical history coincides with large variability in platelet counts. Platelet clumping on the blood film indicates the presence of pseudothrombocytopenia, but automated cell counters may not produce this information. Anaesthetists should be aware that, in patients with pseudothrombocytopenia, the platelet count obtained from EDTA sampling bottles may not reflect the *in vivo* status accurately. In some but not all of these patients, *in vitro* platelet clumping may be prevented by using citrated containers. Blood samples should be analysed before prolonged exposure to room temperature has taken place. If this is impracticable, other tests, such as thrombelastography, may be used to reflect the numerical and functional integrity of circulating platelets. Awareness of the phenomenon and knowledge of the underlying physiological principles will enable anaesthetists to manage patients with anticoagulant-induced pseudothrombocytopenia appropriately.

References

1 Despotis GJ, Filos SK, Zoys TN, Hogue CW, Spitznagel E, Lappas DG. Factors associated with excessive postoperative blood loss and hemostatic transfusion requirements: a multivariate analysis in cardiac surgical patients. *Anesth Analg* 1996; **82**: 13–21

2 Wahba A, Rothe G, Lodes H, Barlage S, Schmitz G, Birnbaum DE. Predictors of blood loss after coronary artery bypass grafting. *J Cardiothorac Vasc Anesth* 1997, **11**: 824–7

3 Harker LA, Malpass TW, Branson HE, Hessel II EA, Slichter SJ. Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: acquired transient platelet dysfunction associated with selective α-granule release. *Blood* 1980; **5**; 824–34

4 Dacey LJ, Munoz JJ, Baribeau YR, Johnson ER, Lahey SJ, Leavitt BJ, Quinn RD, *et al.* Reexploration for hemorrhage following coronary artery bypass grafting *Arch Surg* 1998; **133**: 442–7

5 Bizzaro N, Brandalise M EDTA-dependent pseudothrombocytopenia. Association with antiplatelet and antiphospholipid antibodies *Am J Clin Pathol* 1995; **103**: 103–7

6 Bartels PC, Schoorl M, Lombarts AJ. Screening for EDTA-dependent deviations in platelet counts and abnormalities in platelet distribution histograms in pseudothrombocytopenia. *Scand J Clin Lab Invest* 1997; **57**: 629–36

7 Silvestri F, Virgolini L, Savignano C, Zaja F, Velisig M, Baccarani M. Incidence and diagnosis of EDTA-dependent pseudothrombocytopenia in a consecutive outpatient population referred for isolated thrombocytopenia. *Vox Sang* 1995; **68**: 35–9

8 Pegels JG, Bruynes EC, Engelfriet CP, von dem Borne AE. Pseudothrombocytopenia: an immunological study on platelet antibodies dependent on ethylene diamine tetra-acetate. *Blood* 1982; **59**: 157–61

9 Howard L, Shulman S, Sadanandan S, Karpatkin S. Crossed immunoelectrophoresis of human platelet membranes: The major antigen consists of a complex of glycoproteins GPIIb and GPIIIa, held together by Ca^{++} and missing in Glanzmann's *thrombasthenia*. *J Biol Chem* 1982; **257**: 8331–6

10 Kunicki TJ, Pidard D, Rosa JP, Nurden AT. The formation of Ca^{++}-dependent complexes of platelet membrane glycoproteins IIb and IIIa in solution as determined by crossed immunoelectrophoresis. *Blood* 1981; **58**: 268–78

11 Peterson P, Hayes TE, Arkin CF, Bovill EG, Fairweather RB, Rock WA, *et al.* The preoperative bleeding time test lacks clinical benefit. *Arch Surg* 1998; **133**: 134–9

12 Spiess BD, Tuman KJ, McCarthy RJ, DeLaria GA, Schillo R, Ivankovitch AD. Thrombelastography as an indicator of post-cardiopulmonary bypass coagulopathies. *J Clin Monit* 1987; **3**: 25–30

13 Anonymous. Practice guidelines for blood component therapy. A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. *Anesthesiology* 1996; **84**: 732–47

14 Schrezenmeier H, Muller H, Gunsilius E, Heimpel H, Seifried E. Anticoagulant-induced pseudothrombocytopenia and pseudoleucocytosis. *Thromb Haemost* 1995; **73**: 506–13

15 Bizzaro N EDTA-dependent pseudothrombocytopenia: a clinical and epidemiological study of 112 cases, with 10-year follow-up. *Am J Hematol* 1995; **50**: 103–9

16 Dalamangas LC, Slaughter TF. Ethylenediaminetetraacetic acid-dependent pseudothrombocytopenia in a cardiac surgical patient. *Anesth Analg* 1998; **86**: 1210–1

17 Mallett SV, Cox DJA. Thrombelastography. *Br J Anaesth* 1992; **69**: 307–13

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Oesophageal perforation following perioperative transoesophageal echocardiography

S. R. Massey[1]*, A. Pitsis[2], D. Mehta[3] and M. Callaway[4]

[1]Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary, [2]Bristol Heart Institute, Bristol Royal Infirmary, [3]Department of Cardiothoracic Surgery, Bristol Royal Infirmary and [4]Department of Radiology, Bristol Royal Infirmary, Bristol BS2 8HW, UK

**Corresponding author*

Transoesophageal echocardiography (TOE) is being used more often by cardiothoracic anaesthetists for the perioperative management of cardiac problems. Reports of iatrogenic oesophageal perforation by instrumentation of the oesophagus are increasing.[1] Although TOE is considered safe,[2 3] it may be more risky during surgery, because the probe is passed and manipulated in an anaesthetized patient. It may be in place for several hours so the risk of mucosal pressure[4] and thermal damage is increased. Patients on cardiopulmonary bypass are also fully anticoagulated. We describe a case of oesophageal perforation following insertion of the TOE probe in a patient with gross cardiomegaly. Oesophageal distortion by cardiac enlargement may increase the risk of oesophageal perforation. Difficulty in passage of the TOE probe should be regarded with suspicion and withdrawal should be contemplated because the symptoms of oesophageal perforation are often delayed[5] and non-specific.[1] Delay in investigation, diagnosis and treatment will increase morbidity and mortality.[6–8]

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Keywords: transoesophageal heart echocardiography;, complications, oesophageal perforation

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Transoesophageal echocardiography (TOE) is being used increasingly by cardiothoracic anaesthetists in the UK. We describe a case of iatrogenic oesophageal perforation after perioperative insertion of a TOE probe in a patient with gross cardiomegaly.

Case report

A 59-yr-old woman with severe rheumatic mitral valve disease was admitted for mitral valve repair or replacement and tricuspid valve repair. She had severe mitral regurgitation, a dilated and severely globally impaired left ventricle, pulmonary hypertension (52/28 mm Hg) and normal coronary arteries. Chest x-ray showed gross cardiomegaly with a heart:chest ratio of 1 and a splayed carina (Fig. 1).

She had audible inspiratory stridor during normal conversation but gave no history of regurgitation or dysphagia. After peripheral venous and arterial cannulation, anaesthesia was induced with fentanyl, midazolam and etomidate. A right internal jugular central venous catheter and a Swan–Ganz introducer sheath were then inserted. The TOE probe (Hewlett-Packard Omniplane) was inserted into the oesophagus easily under direct vision using a laryngoscope. Resistance to passage was felt at 30 cm and no effort was made to pass the probe further. TOE at this level revealed a huge left atrium 16.5 cm in diameter (Figs 2, 3). Further preoperative assessment was made using transthoracic echocardiography.

The mitral valve annulus was 45 mm diameter. The mitral valve was replaced by a Medtronic Intact porcine bioprosthesis, with preservation of the posterior leaflet. A very thin friable left atrial wall was noted and there was considerable bleeding from the left atriotomy, which was controlled with difficulty. The cardiopulmonary bypass time was 2 h 48 min. Epinephrine, norepinephrine and enoximone were used during separation from bypass. She was extubated the following morning. A nasogastric tube was not used after the operation.

She progressed well and was eating normally until she complained of severe right pleuritic pain on the fourth postoperative day. Chest x-ray showed a large right pleural effusion which drained 2.5 litres of milky fluid. Later the same day she became unwell with hypotension, dyspnoea, oliguria and rapid atrial fibrillation. Mechanical ventilation was commenced. By the next day, 7000 ml of increasingly thick, offensive fluid had drained from the chest drain. At oesophagoscopy, a 5-cm oesophageal tear was found, starting 34 cm from the incisors, with an adjacent abscess cavity.

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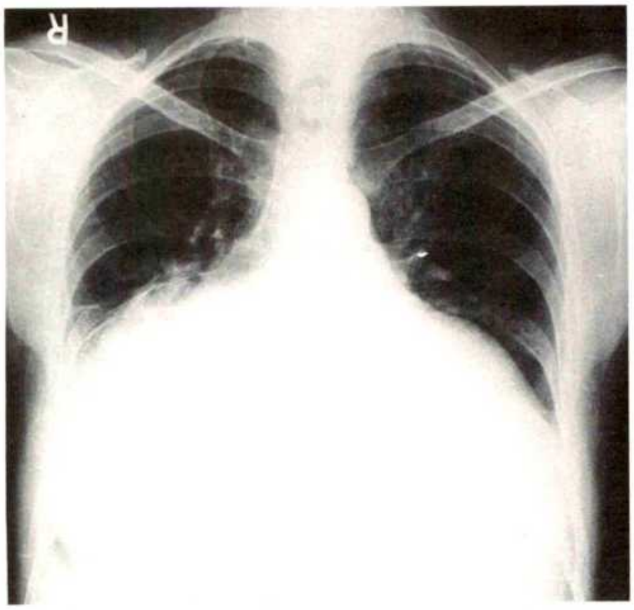

Fig 1 Chest radiograph demonstrating gross cardiomegaly with heart:chest ratio of 1 and a splayed carina.

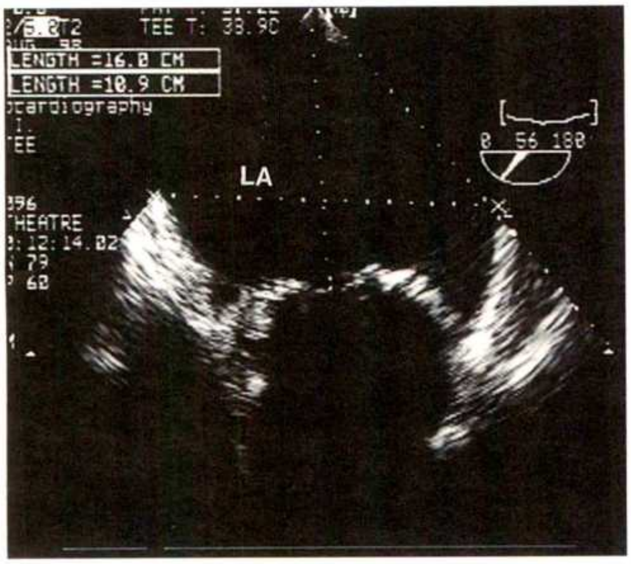

Fig 2 Transoesophageal echocardiogram with multiplanar probe at the level of the left atrium and left atrial appendage. The size of the atrium is 16.0×10.9 cm (see centimetre measurement marks). LA = left atrium.

At surgery, the oesophagus was friable, oedematous and displaced laterally, stretched around the enlarged left atrium. Despite defunctioning of the oesophagus by a cervical oesophagostomy, gastrostomy and drainage of the mediastinum, the patient deteriorated and died on the ninth day after the operation.

At post-mortem the oesophagus was noted to be very thin and friable, with associated inflammation around the tear. The oesophagus was distended around the left atrium with fibrosis and tethering.

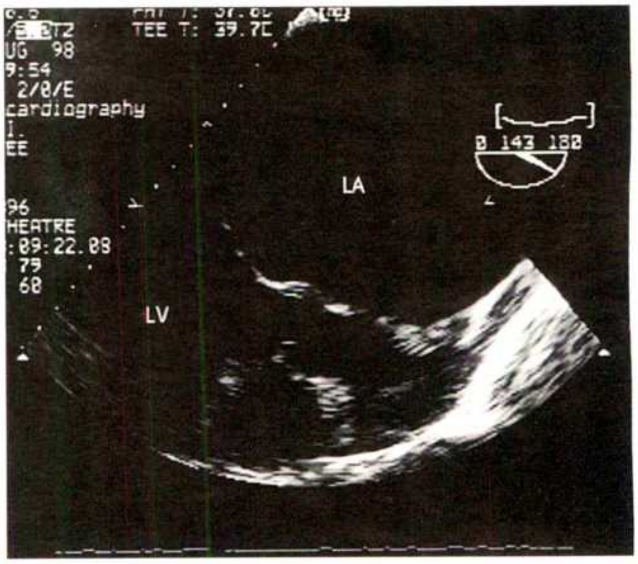

Fig 3 Transoesophageal echocardiogram with the multiplanar probe at the level of the left atrium and left atrial appendage. The plane of imaging has been rotated through 90°, producing a longitudinal view of the grossly enlarged left atrium. LA = left atrium; LV = left ventricle.

Discussion

TOE is widely used in North America for cardiac surgical management. The American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force practice guidelines define three categories of perioperative TOE indications[9 10] (Table 1). Each category is defined by the degree to which expert opinion, and evidence, show that TOE can improve outcome. TOE is being used more by anaesthetists in the UK. The indications for our use of TOE were category IiA and IiB. TOE is considered to be safe.[2 3] In a multicentre study of 10 219 successful TOE probe insertions[2] there was only one death, from an invasive lung tumour and haemorrhagic complications. However, of the total studied (10 419) only 11.9% were perioperative. In perioperative cardiac TOE the probe remains *in situ* for several hours, during which time the patient is fully anticoagulated on cardiopulmonary bypass. In addition, the probe is inserted and manipulated in an anaesthetized patient who cannot indicate discomfort. Urbanowicz and colleagues found that the TOE probe may cause mucosal ischaemia by direct pressure of up to 60 mm Hg.[4] Leaving the tip flexed and locked for periods of time may also increase any ischaemia. When active, the probe becomes warm and could cause damage if it were used continuously for a long time.

There are seven published cases,[2 11–16] including one death, of gastrointestinal tract damage from TOE. Three were mucosal lacerations occurring after uneventful perioperative TOE.[11–13] All presented immediately after operation with blood aspirated from a nasogastric tube, passed routinely, after removal of the TOE probe. Two cases of haemorrhage occurred from oesophageal contusions.[2 14] These presented 30 h and 4 days after non-perioperative

Table 1 Indications for the use of TOE[10]

Category I: supported by the strongest evidence or expert opinion
- i Perioperative
  - A Haemodynamic disturbance
  - B Valve repair
  - C Congenital heart surgery
  - D Thoracic aortic aneurysms, dissection or disruption
  - E Hypertrophic obstructive cardiomyopathy
  - F Endocarditis
  - G Assessment of aortic valve function in repair of aortic dissection
  - H Intensive care unit investigation of unstable patients with unexplained haemodynamic disturbances, suspected valve disease or thromboembolic problems
  - I Pericardial window procedures
  - J Minimally invasive cardiac surgery

Category II: supported by weaker evidence and expert consensus
- i Perioperative
  - A Patients with increased risk of myocardial infarction
  - B Patients with increased risk of haemodynamic disturbance
  - C Monitoring placement and function of assist devices
  - D Assessment of patients with suspected acute thoracic dissections aneurysms or disruption
- ii Intraoperative
  - A Assessment of repair of cardiac aneurysm
  - B Evaluation of removal of cardiac masses
  - C Detection of foreign bodies
  - D Detection of air emboli during cardiotomy, heart transplantation and upright neurosurgical procedures
  - E Intracardiac thrombectomy
  - F Pulmonary embolectomy
  - G Suspected cardiac trauma
  - H Repair of thoracic aortic dissection without suspected aortic valve involvement
  - I Detection of aortic atheromatous disease or other sources of aortic emboli
  - J Evaluation of pericardial surgery
  - K Evaluation of anastomotic sites during heart and/or lung transplantation

Category III. little scientific or expert opinion support
- i Intraoperative
  - A Evaluation of myocardial perfusion, coronary artery anatomy, graft patency
  - B Repair of cardiomyopathies (other than hypertrophic obstructive cardiomyopathy)
  - C Uncomplicated endocarditis during non-cardiac surgery
  - D Monitoring for emboli during orthopaedic procedures
  - E Assessment of repair of thoracic aortic injuries
  - F Uncomplicated pericarditis
  - G Evaluation of pleuropulmonary disease
  - H Monitoring of cardioplegia administration
- ii Placement of monitors
  - A Monitoring placement of intra-aortic balloon pumps
  - B Automatic implantable cardiac defibrillators
  - C Pulmonary artery catheters

TOE. The former occurred during anticoagulation and the latter after thrombolysis for a valve thrombosis. Two patients had perforations, one in the hypopharynx[15] and one at the gastroesophageal junction.[16] The hypopharyngeal perforation occurred as the TOE probe was inserted after sternotomy for a cardiac operation. The diagnosis was made immediately because the probe appeared in the operative field. The perforation tract was drained and surgical closure of the perforation followed the next day. The patient was discharged home on the 40th postoperative day. The gastroesophageal junction perforation occurred despite a seemingly normal perioperative TOE. The patient first complained of nausea at 04:00 am the morning after an aorto-bifemoral graft. At 06:00 am the patient developed abdominal pain and coffee-ground emesis. A nasogastric tube was passed and a further 600 ml was aspirated. A limited gastrointestinal contrast study led to the diagnosis of a perforation in the afternoon of the first postoperative day. Despite a thoracoabdominal oesophagogastrectomy, the patient died on the seventh postoperative day.

Iatrogenic oesophageal injury is the most common cause of oesophageal injury, accounting for 73% of reported cases.[1] It is associated with high morbidity and mortality.[6 7] Unfortunately, iatrogenic oesophageal perforations are increasing.[1 7] Unless there is a very high index of suspicion, the diagnosis of perforation is often delayed or missed.[1 5] Meckler's triad, of vomiting, pain and subcutaneous emphysema, relating to spontaneous oesophageal perforation, is often absent. The patients are often symptom-free for several hours and 33% of initial chest x-rays are normal.[5] Oesophagography is the most sensitive investigation, demonstrating over 90% of perforations.[5 7] This may be improved by performing the investigation in the lateral decubitus position.[17]

A delay in diagnosis increases morbidity and mortality[6 7], although the 24-h watershed after which surgical outcome is poorer has been brought into doubt by a recent report[1] with 10% mortality compared with the normal 25%.[8]

Other complications of TOE include bradycardia,[18] ventricular tachycardia,[2] third-degree heartblock,[2] atrial fibrillation,[2] angina,[2] upper airway obstruction,[19 20] fatal embolization of the right atrial mass,[21] hypoxia,[2] bronchoconstriction,[2] and death from cardiac tamponade during TOE for aortic aneurysm dissection.[22] There is also an association between perioperative TOE and postoperative swallowing dysfunction.[23]

Our patient died of an oesophageal perforation caused, presumably, by attempted passage of a TOE probe. Later discussion with the family revealed that the patient had actually complained of dysphagia. This is a contraindication to TOE, as is any oesophageal or gastric disease.[10 24] This was unfortunately not noted by the anaesthetic or surgical assessments.

Severe cardiac enlargement can displace and thin the oesophageal wall. Oesophageal barium studies might indicate increased risk of oesophageal perforation in these patients. Should resistance to passage of the TOE occur, the probe should be withdrawn from this position.

Between active imaging, the TOE should be left *in situ*, in an unlocked position, with the probe head non-active to prevent thermal injury.

Oesophageal perforation has a better prognosis if diagnosed and treated early.[6] Iatrogenic perforations do not give symptoms for many hours, and the first postoperative chest x-rays are often normal.[5] Our patient was symptom-free until the fourth day after operation, when she was eating and drinking normally.

Difficulty in passing the TOE probe, or a bloodstained gastric aspirate after removal of the probe, should indicate early investigation, diagnosis and surgical treatment to reduce the high risk of morbidity and mortality.

References

1 Lawrence DR, Ohri SK, Moxon RE, Townsend ER, William-Fountain S. Iatrogenic oesophageal perforations: a clinical review. *Ann R Coll Surg Engl* 1998; **80**: 115–8

2 Daniel WG, Erbel R, Kasper W, *et al*. Safety of transesophageal echocardiography. A multicenter survey of 10,419 examinations. *Circulation* 1991; **83**: 817–21

3 Chee TS, Quek SSS, Ding ZP, Chua SM. Clinical utility, safety, acceptability and complications of transoesophageal echocardiography (TEE) in 901 patients. *Singapore Med J* 1995; **38**: 479–83

4 Urbanowicz JH, Kernoff RS, Oppenheim G, Parnagian E, Billingham ME, Popp RL. Transesophageal echocardiography and its potential for esophageal damage. *Anesthesiology* 1990; **72**: 40–3

5 Flynn AE, Verrier ED, Way LW, Thomas AN, Pellegrini CA. Esophageal perforation. *Arch Surg* 1989; **124**: 1211–5

6 Attar S, Hankins JR, Suter CM, Coughlin TR, Sequeira A, McLaughlin JS. Esophageal perforation: a therapeutic challenge. *Ann Thorac Surg* 1990; **50**: 45–51

7 Bladergroen MR, Lowe JE, Postlethwait RW. Diagnosis and recommended management of esophageal perforation. *Ann Thorac Surg* 1986; **42**: 235–9

8 Bufkin BL, Miller JI, Mansour KA. Esophageal perforation: emphasis on management. *Ann Thorac Surg* 1996; **61**: 1447–52

9 A report by the American Society of Anaesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force. Practice guidelines for perioperative transesophageal echocardiography. *Anesthesiology* 1996; **84**: 986–1006

10 Working Party of the Association of Cardiothoracic Anaesthetists (ACTA) Transoesophageal Echocardiography (TOE) Sub committee. *Cardiothoracic perioperative transoesophageal echocardiography*. ACTA publication April 1999; 19–20

11 Dewhirst WE, Stragand JJ, Fleming BM. Mallory–Weiss tear complicating intraoperative transesophageal echocardiography in a patient undergoing aortic valve replacement. *Anesthesiology* 1990; **73**: 777–8

12 Latham P, Hodgins LR. A gastric laceration after transesophageal echocardiography in a patient undergoing aortic valve replacement. *Anesth Analg* 1995; **81**: 641–2

13 Kihara S, Mizutani T, Shimizu T, Toyooka H. Bleeding from a tear in the gastric mucosa caused by transoesophageal echocardiography during cardiac surgery: effective haemostasis by endoscopic argon plasma coagulation. *Br J Anaesth* 1999; **82**: 948–50

14 Polhamus CD, Werth TE, Clement DJ, Keogh M, Lewis P. Gastrointestinal bleeding complicating transesophageal echocardiography. *Endoscopy* 1993; **25**: 198–9

15 Spahn DR, Schmid S, Carrel T, Pasch T, Schmid ER. Hypopharynx perforation by a transesophageal echocardiography probe. *Anesthesiology* 1995; **82**: 581–3

16 Karesch ED, Sivarajan M. Gastroesophageal perforation after intraoperative transesophageal echocardiography. *Anesthesiology* 1996; **85**: 426–8

17 DeMeester TR. Perforation of the esophagus. *Ann Thorac Surg* 1986; **42**: 231–2

18 Suriani RJ, Tzou N. Bradycardia during transesophageal echocardiographic probe manipulation. *J Cardiothorac Vasc Anesth* 1995; **9**: 347

19 Zestos MM, Chehade M, Mossad E. A transesophageal echocardiography probe causes airway obstruction in an older child. *J Cardiothorac Vasc Anesth* 1998; **12**: 65–6

20 Saphir JR, Cooper JA, Kerbavez RJ, Larson SF, Schiller NB. Upper airway obstruction after transesophageal echocardiography. *J Am Soc Echocardiogr* 1997; **10**: 977–8

21 Cavero MA, Cristobal C, Gonzalez M, Gallego JC, Oteo JF, Artaza M. Fatal pulmonary embolization of a right atrial mass during transesophageal echocardiography. *J Am Soc Echocardiogr* 1998; **11**: 397–8

22 Silvey SV, Stoughton TL, Pearl W, Collazo WA, Belbel RJ. Rupture of the outer portion of aortic dissection during transesophageal echocardiography. *Am J Cardiol* 1991; **68**: 286–7

23 Hogue CW, Lappas GD, Creswell LL, *et al*. Swallowing dysfunction after cardiac operations. *J Thorac Cardiovasc Surg* 1995; **110**: 517–22

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Mallory–Weiss tear following cardiac surgery: transoesophageal echoprobe or nasogastric tube?

A. J. De Vries*, J. M. A. A. van der Maaten and R. R. P. Laurens[1]

Departments of Anaesthesiology and [1]Cardiothoracic Surgery, University Hospital Groningen, The Netherlands

**Corresponding author: Department of Anaesthesiology, University Hospital Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands*

A case of fatal upper gastrointestinal bleeding from a Mallory–Weiss tear after transoesophageal echocardiography during cardiac surgery is reported. After the echocardiographic examination, which is considered a safe procedure, a nasogastric tube was inserted which immediately revealed bright red blood. Eventually the patient lost 9 litres of blood. The role of the echoprobe and the nasogastric tube in causing the Mallory–Weiss tear is discussed. Although

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this case is not conclusive about the mechanism of oesophageal damage, it is suggested that the safety recommendations for transoesophageal echocardiography also apply for instrumentation of the oesophagus with a nasogastric tube after the transoesophageal echocardiographic examination.

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Transoesophageal echocardiography (TOE) is increasingly used in cardiology and cardiac surgery with few reported complications. In cardiological practice TOE is considered to be a short, semi-invasive diagnostic procedure with a complication risk of 0.5–1% in large series.[1 2] Although most complications are usually transient (e.g. cardiac dysrhythmias, hypotension, dysphagia and laryngospasm), upper gastrointestinal bleeding is potentially dangerous, especially in the setting of cardiac surgery because of the anticoagulation and coagulopathy associated with cardiopulmonary bypass (CPB). The increased contact time between the oesophagus and the TOE probe in the anaesthetized patient during surgery and the longer duration of a flexed probe position for continuous monitoring of left ventricular function may provoke oesophageal mucosal damage. However, overt upper gastrointestinal bleeding following TOE during cardiac surgery has rarely been described.[3 4] We present a patient with fatal massive bleeding from a distal oesophageal lesion, diagnosed as a Mallory–Weiss tear, which occurred following TOE monitoring for cardiac surgery.

Case report

A 74-yr-old man underwent coronary artery bypass grafting for progressive three-vessel disease. He had moderate chronic obstructive pulmonary disease and had suffered a myocardial infarction 1 yr earlier. The preoperative transthoracic echocardiogram showed a moderately impaired left ventricular function. The patient denied a history of coagulopathy, alcohol abuse or gastrointestinal complaints, including oesophageal disease. Medication consisted of lisinopril, bisoprolol, furosemide, aspirin, ipratropium bromide and budesonide. Aspirin was stopped 2 days before admission to hospital. After induction of anaesthesia, a TOE multiplane probe (Vingmed, Sonotron, Zoetermeer, The Netherlands, tip dimensions: diameter 15.7 mm, length 44 mm) covered by a well-lubricated protective sheath was uneventfully inserted. The controls of the probe were in the neutral position to allow the probe to follow the natural course of the oesophagus. Images of the heart were obtained from the standard positions (mid-oesophageal and transgastric views). The angular fixation device to lock the probe was not used. The acoustic power control of the echomachine was in the default setting.

Revascularization of the myocardium was performed with a left internal mammary artery and a saphenous vein graft. TOE was used to guide weaning from CPB which necessitated ionotropic support (dopamine 10 $\mu g\ kg^{-1}\ min^{-1}$). Heparin action was reversed with protamine which resulted in an activated clotting time of 107 s, comparable to the pre-CPB value. No signs of active bleeding existed in the surgical field. At the end of the operation, no gross fluid levels were seen in the stomach and the TOE probe was carefully removed after ~ 2.5 h. It was perfectly clean without any sign of blood. Thereafter, a 16F nasogastric tube at room temperature (Sherwood Medical, 's Hertogenbosch, The Netherlands) was inserted. The first attempt failed to pass the pharyngeal structures, but a second attempt resulted in a smooth introduction without obvious resistance. Suction was applied to verify the position and immediately 100 ml of bright red blood without clots was seen. The patient was transferred to the intensive care unit where again suction was applied to the nasogastric tube and another 500 ml of bright red blood was removed. The bleeding was refractory to therapy which consisted of iced saline flush, and resulted in a blood loss of 3 litres in the next 2 h. Endoscopy was performed and demonstrated small superficial upper gastric and prepyloric erosions, which could not be identified as a bleeding site, and several haematomas without sign of recent bleeding in the proximal oesophagus. At the gastro-oesophageal junction a bleeding lesion was seen in the wall of the oesophagus, which was diagnosed as a Mallory–Weiss tear and was infiltrated with 5 ml of adrenalin solution (100 $\mu g\ ml^{-1}$). Because the bleeding continued, endoscopy was repeated and it was decided to insert a Sengstaken tube. Gradually the bleeding stopped after a total blood loss of 9 litres. No bleeding was observed from other sites and laboratory tests showed normal clotting values (APTT 29 s, PT 17 s, fibrinogen 1.5 $g\ l^{-1}$). After 5 days, endoscopy was repeated showing no signs of haematomas in the proximal oesophagus and varices grade 1 in the distal oesophagus. The gastro–oesophageal junction was not seen due to a large black clot. The gastric mucosa was normal and no signs of active bleeding were present. Secondary to the concomitant massive transfusion, the patient developed a respiratory distress syndrome, a low cardiac output state and renal failure. Eventually the patient died on the 90th postoperative day due to multi-organ failure.

Discussion

This case describes a patient with massive bleeding from a Mallory–Weiss tear, which occurred following TOE during cardiac surgery. Mallory–Weiss tears occur at the gastro–oesophageal junction, indicating that this is a vulnerable area for mucosal lesions. Iatrogenic Mallory–Weiss tears resulting from upper gastrointestinal endoscopy have an incidence of 0.07–0.5%.[3 5 6] In most patients, bleeding from these tears stops spontaneously and is managed non-surgically, but blood loss may be considerable.[7] TOE is a rapidly evolving technique and we use it in our institution as a routine technique for all cardiac procedures according to the recently published Practice Guidelines for Perioperative TOE, category I and II.[8] Our patient met the criteria with his previous myocardial infarction, his impaired left ventricular function and his planned myocardial revascularization. TOE is considered a safe technique with few serious complications. Following TOE during cardiac surgery the incidence of occult blood in postoperative nasogastric aspirate is ~50%, which is even lower than the incidence of occult blood in control patients who had not undergone TOE.[9] However, the low incidence of significant gastrointestinal bleeding associated with TOE is apparent from the few case reports of this complication.[1 3 4 10]

What could have caused the Mallory–Weiss tear in our patient? The insertion of the TOE probe was uneventful and no excessive force was used to advance the probe, nor was the probe advanced with a flexed tip, thereby minimizing the risk of injury to the oesophagus during insertion. A review of the examination tape revealed no gross fluid levels in the stomach at the end of surgery and the protective sheath of the TOE probe was not bloodstained on removal, indicating that no significant bleeding up to that moment existed. It seems highly unlikely that all of the blood could have been wiped off the protective sheath by removal of the TOE probe from the oesophagus. Immediately after removal of the TOE probe a nasogastric tube was inserted as is routine in postoperatively ventilated cardiac patients to achieve gastric decompression and to prevent the accumulation of gastric contents due to their opioid anaesthesia. The insertion of the nasogastric tube was followed by the aspiration of bright red blood. This sequence of instrumentation of the oesophagus is basically the same as in two other case reports on significant gastrointestinal bleeding after an intraoperative TOE examination,[3 4] but in those cases the bleeding was attributed solely to the instrumentation of the oesophagus with the TOE probe. Although the insertion of a nasogastric tube may have contributed to oesophageal and gastric mucosal damage, it is difficult to assess the magnitude of contribution to laceration or tearing.

Many of the reported complications of TOE could result from pressure exerted by the tip of the probe on the oesophagus and the stomach. It has been shown that generally oesophageal contact pressure exerted by a TOE probe is low and does not exceed 17 mm Hg in various positions, but that unexplained high pressure up to 60 mm Hg can occur.[11] Moreover, it has been shown that in obtaining the left ventricular short axis view in 73% of patients the tip of the TOE probe was located in the stomach, in 14% at the gastro–oesophageal junction and in 13% in the oesophagus.[12] To obtain this short axis view the TOE probe has to be flexed, and puts the gastro–oesophageal junction, which acts as a hinge for the TOE probe, at risk of pressure lesions. This raises concern for the apical four-chamber view which requires extreme flexion and may result in gastric laceration.[4] In our patient, small upper gastric erosions were observed at endoscopic examination, but the apical four-chamber view was not used. Although the average contact time of the TOE probe during cardiac surgery is longer than in cardiological practice, a long contact time has not been shown to cause oesophageal mucosal damage in animal studies.[11 13] Thermal injury as a contributing factor[10] is unlikely, as the acoustic power was in the default setting, the ultrasound was used only for short examinations and the echoprobe was protected from temperatures exceeding 40°C by automatic shut-down. The effect of a latex protective sheath covering the TOE probe and its possible folds on the mucosa of the oesophagus is unknown. Residual coagulopathy after cardiac surgery is a possible contributing factor, but after reversal of heparin a normal clotting was achieved. The same applies for the residual effect of the use of aspirin. Furthermore, TOE can even be safely performed in patients undergoing liver transplantation, known for their coagulopathies and oesophageal varices.[14]

In conclusion, the potential for oesophageal damage from TOE examination during cardiac surgery is illustrated in a patient with fatal bleeding from a Mallory–Weiss tear. Although our case is not conclusive about the mechanism of oesophageal damage, instrumentation of the oesophagus with either a TOE probe or a nasogastric tube after TOE probe removal is a potential risk factor for oesophageal bleeding after TOE examination during cardiac surgery. To ensure the safety of TOE, several basic rules should be observed: inspection of the probe prior to insertion for cleanliness and structural integrity; gentle introduction and positioning of a well-lubricated probe; avoidance of advancing the probe forcefully or manipulation with the tip in a locked position or leaving the tip flexed for a prolonged period of time. Therefore, we suggest that the recommendations for safety in TOE (including gentle insertion and positioning) also apply for instrumentation of the oesophagus with a nasogastric tube after TOE examination.

References

1 Daniel WG, Erbel R, Kasper W, *et al.* Safety of transesophageal echocardiography; a multicenter survey of 10419 examinations. *Circulation* 1991; **83**: 817–21

2 Chan KL, Cohen GI, Suchowski RA, Baird MG. Complications of transesophageal echocardiograpgy in ambulatory adult patients: analysis of 1500 consecutive examinations. *J Am Soc Echocardiogr* 1991; **4**: 577–82

3 Dewhirst WE, Stragand JJ, Fleming BM. Mallory–Weiss tear complicating intraoperative transesophageal echocardiography in a patient undergoing aortic valve replacement. *Anesthesiology* 1990; **73**: 777–8

4 Latham P, Hodgins LR. A gastric laceration after transesophageal echocardiography in a patient undergoing aortic valve replacement. *Anesth Analg* 1995; **81**: 641–2

5 Penston JG, Boyd EJS, Wormsley KG. Mallory–Weiss tears occurring during endoscopy: a report of seven cases. *Endoscopy* 1992; **24**: 262–5

6 Montalvo RD, Lee M. Retrospective analysis of iatrogenic Mallory–Weiss tears occurring during upper gastrointestinal endoscopy. *Hepatogastroenterology* 1996; **43**: 174–7

7 Harris JM, DiPalma JA. Clinical significance of Mallory–Weiss tears. *Am J Gastroenterol* 1993; **88**: 2056–8

8 Thys DM, Abel M, Bollen BA, Cahalan MK, *et al.* Practice guidelines for perioperative transesophageal echocardiography. A report by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography. *Anesthesiology* 1996; **84**: 986–1006

9 Hulyalkar AR, Ayd JO. Low risk of gastroesophageal injury associated with transesophageal echocardiography during cardiac surgery. *J Cardiothorac Vasc Anesth* 1993; **7**: 175–7

10 Kharasch ED, Sivarajan M. Gastresophageal perforation after intraoperative transesophageal echocardiography. *Anesthesiology* 1996; **85**: 426–8

11 Urbanowicz JH, Kernoff RS, Oppenheim G, *et al.* Transesophageal echocardiography and its potential for esophageal damage. *Anesthesiology* 1990; **72**: 40–3

12 Orihashi K, Hong Y, Sisto DA, Goldiner PL, Oka Y The anatomical location of the transesophageal echocardiographic transducer during a short-axis view of the left ventricle. *J Cardiothorac Vasc Anesth* 1990; **4**: 726–30

13 O'Shea JP, Southern JF, D'Ambra MN, Margo C, *et al* Effects of prolonged transesophageal echocardiographic imaging and probe manipulation on the esophagus An echocardiographic and pathologic study. *J Am Coll Cardiol* 1991, **17**: 1426–9

14 Suriani RJ, Cutrone A, Feierman D, Konstadt S. Intraoperative transesophageal echocardiography during liver transplantation. *J Cardiothorac Vasc Anesth* 1996; **10**: 699–707

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EQUIPMENT

The LMA 'ProSeal'—a laryngeal mask with an oesophageal vent

A. I. J. Brain[1]*, C. Verghese[1] and P. J. Strube[2]

[1]*Department of Anaesthesia, Royal Berkshire Hospital, Reading, Berkshire RG1 5AN and*
[2]*Department of Anaesthesia, Wycombe General Hospital, Queen Alexandra Road, High Wycombe, Buckinghamshire HP1 2TT, UK*

**Corresponding author: 1, Princes Street, Reading RG1 4EG, UK*

We describe a new laryngeal mask airway (LMA) that incorporates a second tube placed lateral to the airway tube and ending at the tip of the mask. The second tube is intended to separate the alimentary and respiratory tracts. It should permit access to or escape of fluids from the stomach and reduce the risks of gastric insufflation and pulmonary aspiration. It can also determine the correct positioning of the mask. A second posterior cuff is fitted to improve the seal. A preliminary crossover comparison with the standard mask in 30 adult female patients showed no differences in insertion, trauma or quality of airway. At 60 cm H_2O intracuff pressure, the new LMA gave twice the seal pressure of the standard device ($P<0.0001$) and permitted blind insertion of a gastric tube in all cases. It is concluded that the new device merits further study.

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This paper describes a new type of laryngeal mask airway (LMA) incorporating a drainage tube (LMADT). The main aim of the drainage tube is to enhance the safety and the scope of the device, particularly when used with positive pressure ventilation.

Evolution of the concept

The standard LMA has been successful because it usually requires little skill to achieve a patent airway.[1] Suboptimal insertion or fixation of the LMA may allow its distal end to lie anywhere from the nasopharynx[2] to the rima glottidis,[3 4] yet often the airway remains clinically clear. However, the mask was designed to lie with its distal end wedged against the upper oesophageal sphincter (UOS). Any other position is intrinsically unstable for anatomical reasons, as the shape of the mask is an imitation of the pocket-like hypopharynx in which it is intended to lie.

This instability may allow movement during anaesthesia or recovery. A recent report[5] described 82 out of 283 female patients in whom the LMA had rotated onto its side. In addition, mismatch between the mask and pharyngeal contours may result in an inadequate seal,[6] causing the anaesthetist to increase intracuff pressure, which can damage superficial nerves. Evidence from cadavers suggests the mask may protect against regurgitation if its tip is correctly wedged against the UOS.[7] However, this position is not always achieved because the UOS is visible in up to 10–15% of patients when a fibrescope is passed down the airway tube.[8 9] Clearly an LMA which allows the user to detect malposition would be advantageous.

In 1983, the inventor noted that if a second tube was placed in the long axis of the mask, with a distal opening at the mask tip and open proximally to the atmosphere, an effective seal could not be achieved against the larynx unless the distal end of the mask, with its open second tube, was sealed against the UOS. An effective seal around the larynx indicated an effective seal of the second tube at the UOS, as otherwise gases would escape through the second tube. As such leakage was easily detected, this double-tube design seemed desirable because it indicated poor mask position (Fig. 1).

The second tube in the device allows a second sealed junction against the UOS, giving continuity with the alimentary tract and isolating it from the airway. Theoretically this should give (i) some channelling of regurgitated gastric contents; (ii) in consequence, less need for effective occlusion of the UOS by the mask tip in the event of regurgitation; (iii) the opportunity to pass a gastric tube through the

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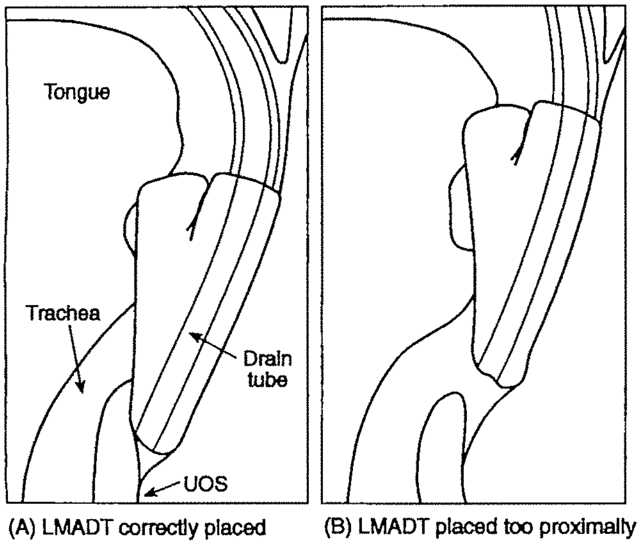

(A) LMADT correctly placed (B) LMADT placed too proximally

LMADT = Laryngeal mask airway with drain tube
UOS = Upper oesophageal sphincter

Fig 1 (A) The LMADT correctly placed. The distal opening of the drainage tube is wedged against the upper oesophageal sphincter, preventing escape of inspired gas through the drainage tube. (B) The LMADT is lying too proximally. The distal end of the drainage tube may communicate with the airway, resulting in gas leaks from the proximal end of the drainage tube.

Table 1 Differences between early (1995) and current models of LMA with drainage tube (DT) ILMA = intubating laryngeal mask airway

Prototype LMA with drainage tube (1995)	**New LMA with drainage tube (1999)**
DT behind airway tube and mask bowl	DT arranged lateral to airway tube
DT runs posterior to mask bowl	DT runs anterior to mask bowl
Mask aperture bars	No mask aperture bars
Distal orifice of DT cut square	Distal orifice of DT cut obliquely
DT not designed to collapse on deflation	DT orifice designed to collapse on deflation
Bowl of mask in same position as standard LMA	Bowl of mask moved posteriorly
Mask is same shape as standard LMA	Mask has posterior extension proximally
Mask has large posterior cuff to increase seal	Mask seal increase achieved partly by deeper bowl, partly by smaller posterior cuff
Not fitted with finger/introducer locating strap	Fitted with finger/introducer locating strap
Not fitted with bite-block	Fitted with integral bite-block
No introducer tool	Introducer tool available
Insertion requires rotation, like Guedel airway	Insertion same as standard LMA (using finger) or same as ILMA (using introducer tool)
Airway tube identical to standard LMA, but stiffened by presence of posteriorly placed DT	Airway tube is wire-reinforced, more flexible than standard LMA

drainage tube; and (iv) avoidance of gastric insufflation during positive pressure ventilation.

A crude prototype incorporating a drainage tube was described in 1995.[10] Important differences from the previous (1995) prototype are summarized in Table 1.

This paper describes a more developed form of the LMADT (LMA ProSeal, LMA Company) and preliminary data obtained from a feasibility study.

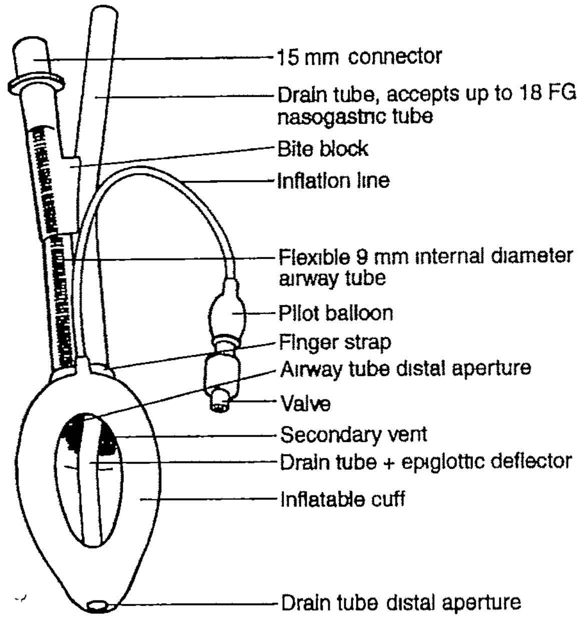
15 mm connector
Drain tube, accepts up to 18 FG nasogastric tube
Bite block
Inflation line
Flexible 9 mm internal diameter airway tube
Pilot balloon
Finger strap
Airway tube distal aperture
Valve
Secondary vent
Drain tube + epiglottic deflector
Inflatable cuff
Drain tube distal aperture

Fig 2 The size 4 LMADT seen from the front.

Device description

Figure 2 shows the LMADT from the front.

Methods

Preliminary clinical data

Study aims

We had only one size of prototype device. We planned a limited comparison of the new LMA with the standard device to assess the following: (i) ease of insertion with or without a special introducer tool; (ii) airway seal pressure at standard intracuff pressure of 60 cm H_2O; (iii) an appropriate patient weight for the single size of trial device available (equivalent to a size 4 LMA); (iv) ease and reliability of insertion of nasogastric tubes up to 18 French gauge

We obtained local ethical committee approval to compare the new device (LMADT) with the standard LMA within the same patient. We studied 30 fasted ASA 1 or 2 adult female patients who had given written informed consent and were undergoing procedures requiring general anaesthesia where a standard size 4 LMA would normally have been chosen. Before starting the study, three investigators, who were of consultant grade, were taught how to use the device by the inventor (AIJB). Each then performed 10 insertions with the index finger and then 10 insertions with the introducer tool, before collecting data from a further 10 patients, in five of whom the insertion tool was used. The device to be used first was selected randomly by opening a sealed envelope. A standard size 4 LMA and the test device were inserted into each patient and inflated to 60 cm H_2O intracuff pressure, using a calibrated aneroid manometer. Insertion using the index finger was identical to the standard insertion technique described in the LMA instruction manual,[11] but insertion using the tool provided was identical to that for the intubating laryngeal mask airway.[12]

Anaesthetic technique and premedication were not standardized, but in all cases patients were paralysed and ventilated and standard monitoring was applied before anaesthesia. Using the anaesthetist's choice of non-depolarizing agent at a dose appropriate for tracheal intubation, neuromuscular block was achieved before insertion of the device. Immediately after insertion and cuff inflation, manual ventilation of the lungs was carried out with the circuit closed to determine (i) whether an expired volume of more than 8 ml kg^{-1} could be achieved, using a Datex Monitor AS/3 (Datex Engstrom, Helsinki, Finland) and, in the case of the test device, (ii) whether leaks occurred up the drainage tube at less than 20 cm H_2O airway pressure. A minimum V_T of 8 ml kg^{-1} was chosen in an attempt to avoid gastric insufflation. Leak detection was sought below a peak airway pressure of 20 cm H_2O as significant leaks up the drainage tube below this level would suggest malposition of the device. For the latter measurement, an in-line manometer was placed immediately proximal to the airway device and a bolus of 0.5–1 ml of lubricant jelly was placed in the proximal orifice of the drainage tube to seal it. The airway pressure at which this bolus was ejected was noted. If such leaks were detected, malposition was diagnosed and a further insertion attempt was made after the device had been deflated carefully. If partial or complete airway obstruction was noted or the minimum expired tidal volume was not achieved despite adequate neuromuscular block, entry of the distal end of the device into the laryngeal vestibule was presumed and the device was removed and reinserted. A maximum of three attempts was permitted with each device, after which the alternative device was used. If neither device could achieve a satisfactory airway, as defined above, the patient's trachea was intubated conventionally.

If a satisfactory airway had been achieved, the selected device was fixed in place with its cuff inflated to 60 cm H_2O. A single within-patient comparative test was carried out under steady-state conditions (before surgical manipulation) to determine the relative seal pressure for each device at which leaks occurred, as follows: the ventilator was switched off, the spill valve closed and pressure allowed to rise in the breathing circuit at 3 litre min^{-1} fresh gas flow, until no further increase in pressure was seen. Circuit pressure was not allowed to increase above 40 cm H_2O and oxygen saturation, measured with finger transmission oximetry (Datex AS/3), was not permitted to fall below 95%. Except when one of the devices had previously failed to provide an airway within three attempts, the device currently in place was then deflated, removed and immediately replaced with the alternative device, after which the measurement was repeated. In the case of the test device, a lubricated nasogastric tube (12–18 French gauge) was inserted blindly down the drainage tube after demonstration of correct device position and after pressure measurements had been made. Suction was applied, the volume of any gastric fluid noted and the catheter removed. Ease or difficulty of placement was noted. Investigators were warned that in no circumstances should force be used in attempting to pass the nasogastric tube.

Before starting the study, we measured the volume of each device at atmospheric pressure and then its static compliance when inflated with up to 30 ml additional air. In patients, we recorded body weight, height (n=20), subjective ease of insertion (1=very easy, 2=easy, 3=difficult, 4=very difficult), volume added to the cuff to achieve an intracuff pressure of 60 cm H_2O, duration of anaesthesia, anaesthetic agents used, whether regurgitation was observed at any time with either device and how this was detected, and any comments by recovery staff regarding the quality of recovery. Removal of the device in all cases was timed to coincide with the return of consciousness, indicated by response to command.

In a subgroup of 20 patients (group 2), further data were recorded: (i) fibre-optic assessment (fibreoptic bronchoscope, FOB) was made to compare views through the LMA and LMADT using a scoring system (1=full view of cords, 2=view of cords partially blocked by epiglottis, 3=only arytenoids visible, 4=no laryngeal structures visible); (ii) the body mass index was also calculated in this group to see whether this was related to seal pressure.

Statistical analysis

To detect a minimum difference of 5 cm H_2O between the two devices, we took interpatient variability as SD=4, based on experience and an empirical finding of a coefficient of variation (CV) of 0.2. Instrumental accuracy was taken as being within a CV of 0.1, giving SD=2. Together, this gives a power of 0.915 when taking 18 readings with each device. Allowing for possible exclusions, we chose to examine a minimum of 20 patients. Data were analysed using the chi-squared test, and $P<0.05$ was taken as statistically significant. Data are reported as mean (range) unless stated otherwise.

Results

Cuff volumes for the LMADT and LMA at atmospheric intracuff pressure were 30 and 25 ml respectively. Progressive inflation with a further 30 ml air gave a mean compliance for each device of 0.36 (0.04–0.02) and 0.13 (0.02–0.01) ml cm H_2O^{-1} respectively.

Twenty patients were recruited from our institution and a further 10 from a second institution. Propofol and Atracurium were used in all patients. The patients had a body weight of 67.5 (50–95) kg, height of 161 (152 –172) cm

Table 2 Fibre-optic scores and ease of insertion for the standard LMA and the LMA with drainage tube (LMADT). Fibre-optic scores 1 = cords fully visible; 2 = cords partly occluded by epiglottis, 3 = only arytenoids visible, 4 = no laryngeal structures visible. Ease of insertion scores: very easy, easy, difficult, very difficult/impossible. Data were analysed with the chi-squared test There were no significant differences between the scores for either feature (P=0 49 for fibre-optic score, P=0 13 for ease of insertion)

Device	Fibre-optic score		Ease of insertion	
	1	2, 3	Very easy	Easy
LMA	13	7	28	2
LMADT	15	5	24	6
Totals	28	12	52	8

and duration of anaesthesia of 48 (20–120) min. No patients were judged difficult for insertion of either device. Two LMA insertions and six LMADT insertions were scored 'easy' as opposed to 'very easy' (P=0.13) (Table 2). The insertion tool did not affect ease of insertion. At an intracuff pressure of 60 cm H_2O, mean seal pressures were twice as high with the LMADT as with the standard LMA: 30 (15–40) compared with 15.8 (10–32) cm H_2O respectively (P<0.0001). There was no relation to body weight (P= 0.7). Mean volume of air injected into the cuff to achieve an intracuff pressure of 60 cm H_2O was 25.9 (16–34) ml for the LMADT and 15.3 (10–25) ml for the LMA. Leaks from the LMADT drainage tube were detected at lung inflation pressures less than 20 cm H_2O in five of 30 patients, but were abolished in all but one of these either by pressing the device more firmly into place (n=2) or by reinsertion (n=2). Obstruction immediately after insertion was diagnosed in one case with the LMA and in two cases with the LMADT, only one of which required reinsertion to correct it. A tidal volume of 8 ml kg^{-1} was achieved in 29 of 30 cases with the LMA and in all cases with the LMADT. No patient required tracheal intubation. A nasogastric tube was inserted through the LMADT drainage tube easily in 28 patients, with difficulty in two. Gastric fluid was aspirated from the stomach in 25 of 30 cases, the volume being 15 ml (0–80). After device removal in the recovery area, a trace of blood was seen on the LMA mask in one and on the LMADT mask in two cases (difference not significant). There were no cases of regurgitation or aspiration.

The relationship between body mass index and seal pressure is shown for the 20 patients in group 2 in Figure 3. There was no significant difference in fibre-optic score (Table 2).

Discussion

We compared a new laryngeal mask incorporating a drainage tube (LMADT) with the standard LMA in a preliminary crossover study in 30 female patients. The following conclusions were drawn.

(i) The LMADT and the standard device are equally easy to insert.

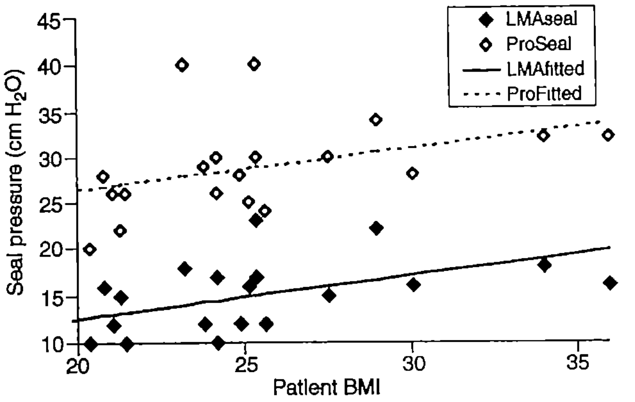

Fig 3 LMA and LMADT seal pressures at 60 cm H_2O intracuff pressure in relation to body mass index (BMI). Slope of line shows the increase in seal pressure for each unit increase in BMI (0.44 cm H_2O). Seal pressure achieved with the LMADT is on average 14 cm H_2O higher than with the LMA (P<0.0001)

(ii) The device can indicate correct or incorrect insertion, but further study will be required to confirm whether this is a reliable diagnostic feature.

(iii) On average, the seal pressure obtained was 10.8 cm H_2O higher than with the LMA. (P<0.0001). It is tempting to relate this finding to the greater compliance of the new device (0.36 compared with 0.13 ml cm H_2O^{-1}). However, at 60 cm H_2O cuff pressure *in vivo*, cuff volumes were less in both devices than measured volumes at atmospheric intracuff pressure *in vitro* (25.9 compared with 30 ml for the LMADT and 15.3 compared with 25 ml for the LMA). Therefore, at 60 cm H_2O intracuff pressure, seals were achieved at inflation volumes lower than those required to expand the silicone walls of the cuff in both cases. We hypothesize that the larger capacity of the new device may give increased seal pressure by allowing the cuff walls to match the contours of the pharyngeal and laryngeal surfaces more effectively.

(iv) Seal pressures are not influenced by body weight over the range studied (P=0.7); however, in 20 patients in whom the body mass index was calculated, an upward trend of seal pressure was noted in both devices (0.44 cm H_2O per body mass index unit, P=0.007), an interesting finding which warrants further investigation.

(v) Nasogastric tube insertion was usually easy, and this appears to be one of the most potentially useful aspects of the new device. However, it was difficult to insert a size larger than 16 French gauge in these preproduction samples.

In summary, the LMADT may offer some advantages over the existing LMA. The ease of nasogastric tube insertion through the new device was interesting. There is no technical reason why the tube could not be guided into place irrespective of the patient's position, once the mask itself is correctly positioned. Positive pressure was easily achieved over a wide weight range in female adults. The value of the drainage tube, to reduce gastric inflation and reduce regurgitation and possible aspiration, needs further assessment.

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References

1. Davies PRF, Tighe SQM, Greenslade GL, Evans GH. Laryngeal mask airway and tracheal tube insertion by unskilled personnel. *Lancet* 1990; **336**: 977–79
2. Molloy AR. Unexpected position of the laryngeal mask airway [letter]. *Anaesthesia* 1991; **46**: 592
3. Nandi PR, Nunn JF, Charlesworth CH, Taylor SJ. Radiological study of the laryngeal mask. *Eur J Anaesth* 1991; **4**: 33–9
4. Goudsouzian NG, Denman W, Cleveland R, Shorten G. Radiologic localization of the laryngeal mask airway in children. *Anesthesiology* 1992; **77**: 1085–9
5. Sellers WFS, Walters BR, Firkin AP. 'Sideways' laryngeal mask airways. *Anaesthesiology* [letter] 1999 **54**: 603
6. Latorre F, Eberle B, Weiler N, Mienert R, Stanek A, Goedecke R, Heinrichs W. Laryngeal mask airway position and the risk of gastric insufflation. *Anesth Analg* 1998; **86**: 867–71
7. Keller C, Brimacombe J, Radler C, Puhringer F. Do laryngeal mask airway devices attenuate liquid flow between the esophagus and pharynx? A randomized controlled cadaver study. *Anesth Analg* 1999; **88**: 904–7
8. Payne J. The use of the fibreoptic laryngoscope to confirm the position of the laryngeal mask [letter]. *Anaesthesia* 1989; **44**: 865
9. Füllekrug B, Pothmann W, Werner C, Schulte am Esch J. The laryngeal mask airway: anesthetic gas leakage and fiberoptic control of positioning. *J Clin Anesth* 1993; **5**: 357–63
10. Brain AIJ, Verghese C, Strube P, Brimacombe J. A new laryngeal mask prototype. *Anaesthesia* 1995; **50**: 42–8
11. Brimacombe JR, Brain AIJ, Berry AM. *The Laryngeal Mask Airway Instruction Manual (UK)*, 4th edn. Intavent, Reading, 1999
12. Brain AIJ, Verghese C. (eds) *The Intubating Laryngeal Mask Instruction Manual* (UK) 2nd edn. Intavent, Reading

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BJA

COMMENTARY

Evidence-based medicine and the Cochrane Collaboration in anaesthesia

A. M. Møller*, A. F. Smith[1] and T. Pedersen

Department of Anaesthesiology, Bispebjerg University Hospital, DK 2400 Copenhagen NV, Denmark.
[1]Department of Anaesthesia, Royal Lancaster Infirmary, Ashton Road, Lancaster, Lancs LA1 4RP, UK
**Corresponding author*

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In 1972, the British epidemiologist Archie Cochrane published his view of the principles on which the delivery of health care should be based.[1] Put simply, he stated that limited resources should be used equitably to provide care of proven benefit. Cochrane promoted randomized controlled trials (RCT) as the most reliable source of evidence on which to base decisions about the effectiveness of health care interventions. He advocated the compilation of a comprehensive catalogue of definitive reviews of scientifically valid clinical trials for each speciality. These regularly updated reviews could be consulted to assist with clinical decision-making. Medical interventions would thus be scientifically based on properly planned and executed clinical trials (distilled where possible into equally scientifically valid reviews) rather than on anecdote, habit, selective experience, faulty memory, or a skewed sample of the relevant clinical trials. The impact of Cochrane's book,[1] *Effectiveness and Efficiency*, was not fully recognized at the time, but it captured the essence of today's evidence-based medicine movement. Cochrane's vision of a reliable, comprehensive and accurate medical database, the Cochrane Library, is approaching reality.

Evidence-based medicine

The Cochrane Collaboration is a major focus of activity and a rich source of information within the evidence-based medicine movement. The term evidence-based medicine (EBM) originated at McMaster University in Canada, and has been defined as 'the conscientious, explicit and judicious use of the best evidence in making decisions about the care of individual patients.[2–4] Thus to practice EBM is to integrate clinical expertize with the best available external evidence from systematic research.[3]

The practice of EBM is described in David Sackett's book, *Evidence-Based Medicine: How to Practice and Teach Evidence-Based Medicine.*[3] The following is a short outline of the five principles of EBM.

Ask a clinical question you can answer

In order to find an answer to your clinical question, the question will have to be clear and well focused. For example, see the following.

(i) Who is the question about? How could you describe a group of patients similar to this particular patient? (E.g. a healthy teenager, an overweight pregnant woman or an elderly person with coronary heart disease.)
(ii) Which treatment or manoeuvre are you considering for the patient? (E.g. type of anaesthesia, route for central venous catheterization or antibiotic in the intensive care unit.)
(iii) What is the desired (or undesired) outcome for the patient? (Reduced postoperative nausea and vomiting, reduced morbidity or mortality, reduced costs.)

A good question will cover these three areas of subject, intervention and outcome, each of equal importance. Failure to frame the question properly will make it harder to find useful and applicable answers. For example, 'Is propofol a better induction agent than thiopental?' contrasted with 'Does propofol lead to fewer unexpected overnight admissions than thiopental after adult day case laparoscopic sterilization?'

Search for evidence

Information technology has undoubtedly made it easier to search the medical literature, and most institutions provide computers that allow electronic searching. Several databases

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should be used when searching for evidence, as overlap between different databases is often not complete.[5] Medline is well known to most doctors, and a subject can be searched by free text and index terms. The Cochrane Library (see later) currently contains 1221 systematic reviews or protocols to reviews, and references to more than 250 000 randomized or clinically controlled trials.

Additionally, EmBase and Biosis as well as other databases can be sought. These databases are available on CD-ROM and the Internet. It is worth remembering that information retrieval is now a complex field in its own right, and the help of a skilled medical librarian or information scientist is invaluable.

Critical appraisal of the evidence

Critical appraisal is the process whereby we attempt to answer two main questions about the material we have retrieved in our search. These are as follows.

(i) Are the results important (useful for you as a clinician)?
If a study concludes that a diagnostic test is inaccurate or that a treatment has only a negligible effect on patient outcome, there is no need to go through the text to appraise the validity of the study. If, however, results are judged to be important, we must go back and ask the following question.

(ii) Are the results valid (close to the truth)?
Several questions have to be posed, for example: Was the design of the study sensible? What was the intervention studied and what was it compared with? If the trial was about treatment or prevention: Was the assignment of patients randomized and was the allocation procedure concealed? Were all the patients who entered the trial accounted for at its conclusion and were they analysed in the groups to which they were randomized?
What outcome was measured and how? Was the outcome assessor blinded? Was a surrogate end point used? (See later.)
Were the statistics used correctly? And finally, were the conclusions which were drawn by the authors supported by the results?

Together, these questions help to judge the clinical applicability of the study results: This process is not new and is already familiar to most doctors. However, emphasis is placed firmly on the needs of the clinician rather than the researcher and on using the medical literature as a means to an end rather than as an end in itself.

Clinical applicability of evidence-based findings

After critical appraisal, some questions remain: How can you integrate this evidence with your own clinical expertise and decide whether and how to incorporate it into the care of your patient? Do these results apply to your patient? Is your patient so different from those in the trial that the results cannot help you? (Can the results be generalizable?) Does the intervention match your patients (and your) preferences? It is then a clinical decision to estimate the potential benefit of the intervention for the individual patient.

Evaluation

After going through the process of applying EBM in patient care, it is necessary to evaluate the process. How well did we succeed in using EBM? Did we ask the right questions? Did we find useful answers? Will we actually use the findings in clinical practice? Is there anything we can do better?

Systematic versus narrative reviews

The narrative or traditional review article has been a common source of answers to clinical problems. There can, however, be serious flaws in the methodology used, as described by Mulrow.[6] She found, in her now classic survey of reviews in general medical journals, that there was usually no description of the search strategy used to find material for inclusion, nor any description of criteria for including or excluding studies. Furthermore, there was seldom any reporting of methods of appraising studies for inclusion, leading to the suspicion that it may not have been conducted, or that trials were included or excluded on arbitrary and subjective grounds. Mulrow argued that failure to include relevant studies might well result in incorrect conclusions in the final review.[6]

A systematic review, on the other hand, is an overview of primary studies that contains an explicit statement of objectives, materials and methods, which has been conducted according to explicit and reproducible methodology. Reviews prepared within the Cochrane Collaboration are systematic and are regularly updated to incorporate new evidence.

The Cochrane Collaboration

The Cochrane Collaboration is an international organization that aims to help people make well-informed decisions about health care by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care interventions.[7] To perform this task, 51 review groups, each covering a specific area of health care, have been established.

Cochrane Anaesthesia Review Group

The idea of forming a Cochrane Anaesthesia Review Group first arose in the autumn of 1997. At that time, anaesthesia was one of the few areas of medical practice not represented within the collaboration. A group of anaesthetists at the Bispebjerg University Hospital in Copenhagen, Denmark began to explore the possibilities of forming a review group. The first meeting was held during the 6th Annual Meeting of the European Society of Anaesthesiologists in 1998; and an international cooperation began. Further meetings for information and recruitment were held at the Annual Meeting of the American Society of Anesthesiologists and at the 6th Cochrane Colloquium in Baltimore (USA) in the autumn of 1998. Finally, it was agreed to establish the Cochrane Anaesthesia Review Group at an exploratory meeting held in Amsterdam 1999. The group was registered with the Cochrane Collaboration on Feb 8, 2000.

Scope and topics

The scope of the Cochrane Anaesthesia Review Group helps to delineate the way in which the Group conceptualizes the topic. As systematic reviews are prepared, this description helps to highlight areas of care where no trials have been identified. The scope covers anaesthesia, perioperative care medicine, intensive care medicine, resuscitation and emergency medicine. The present list of topics for systematic reviews (Table 1) within anaesthesia and intensive care represents clinical practice in relation to current, past and potential interventions for patients undergoing anaesthesia or intensive care. The list is not exhaustive and the group welcomes suggestions.

Applying evidence-based medicine to practice

Evidence-based medicine has had an enormous impact on clinical medicine, attracting both converts and detractors. The basic premise, that clinical decisions should be made on as sound evidence as possible, appears unassailable.[8] Why then would the idea stimulate controversy? Critics have argued that the term 'evidence-based medicine' is logically indistinguishable from the term 'medicine', and have referred to it as a new type of authoritarianism in medicine.[9–11] Another critic of evidence-based medicine, Bruce Charlton, stated, in his review of David Sackett's book,[9] 'The basic error of evidence-based medicine is quite simple. It is that the epidemiological data do not provide the information necessary to treat individual patients.' This may be a point of concern when evidence-based findings and results of meta-analysis are implemented in clinical practice. However, evidence-based medicine is more than scientific results. It has a large component of clinical experience and empathy, which has to be used in conjunction with the evidence in clinical decision-making. Many critics seem to have overlooked this point.

Table 1 Suggestions for topics in anaesthesia and intensive care medicine

(1) Drugs in anaesthesia and intensive care medicine
  - Opioids
  - Potent inhalation agents
  - Intravenous anaesthetics
  - Premedication and sedatives
  - Neuromuscular blocking agents
  - Other drugs

(2) Anaesthesia and medical disease
  - Preoperative evaluation
  - Preoperative treatment (cardiovascular disease, pulmonary disease, endocrinological disease, renal and liver disease, muscular disorders and malignant hyperpyrexia, neurological diseases, other diseases)
  - Medical intervention for perioperative events
    - Circulatory, respiratory, endocrinological, other

(3) Regional anaesthesia
  - Epidural blockade
  - Spinal blockade
  - Peripheral nerve blocks
  - I v/arterial regional anaesthesia
  - Pharmacology of regional anaesthesia

(4) Ambulatory anaesthesia and anaesthesia outside the operating room
  - Anaesthesia for cardioversion
  - Anaesthesia for electroconvulsive therapy
  - Other interventions

(5) Perioperative care medicine
  - Treatment of the anaesthetic patient in the perioperative period
  - Medical intervention
    - Acute postoperative pain therapy
    - Fluid management crystalloids/colloids, blood component therapy
    - Postoperative complications
    - Early nutrition
    - Other interventions

(6) Patients in postanaesthetic unit and intensive care unit
  - Respiratory care· mechanical ventilation, other ventilatory support
  - Circulatory care. haemodynamic management, volume resuscitation, vasopressors
  - Fluid therapy, metabolism, infection control, nutrition

(7) Technology in anaesthesia and intensive care medicine
  - Equipment

(8) Prehospital medicine, resuscitation and emergency
  - Prehospital care interventions
  - Anaesthesia for patients with trauma
  - Acute medical conditions
  - Initial cardiopulmonary stabilization of patients
  - Cardiopulmonary resuscitation
  - Emergency medicine
  - Acute medical conditions, hypothermia

Critics have argued that the whole enterprise is no more than 'cookbook' medicine, and Goodman[12] has stated that it is outright insulting to doctors to suggest that they have not been basing their practice on evidence. But the evidence they traditionally have used may not have been derived from careful scrutiny of published research, in part because there was very little research to draw on. In fact, for much of medical practice including anaesthesia, this is still true. Anaesthesia may be in an unusual position in that much of what we do is not in itself therapeutic, but is designed to facilitate other interventions. An important difference between anaesthesia and other specialities which predominantly treat disease is that in anaesthesia there is very little research performed with real outcomes as end points, as has been stressed by Goodman[13] and Horan [14] Surrogate or intermediate outcomes, such as laboratory findings, arterial pressure or other physiological parameters predominate as the end points of anaesthetic research, possibly reflecting the greater emphasis given to basic sciences in anaesthetic training compared with other specialities. The disadvantages of the use of surrogate outcome measures, as outlined in a systematic review by Gøtzsche and colleagues in 1996,[15] are a drawback when we are seeking evidence to support clinical decisions. Rather than seeing this as a weakness of 'evidence-based anaesthesia', we feel it should encourage us to demand the use of clinically relevant end points where possible in future anaesthetic research.

As there is no evidence that evidence-based medicine provides better medical care than whatever it was that went before, we have to continue the debate and ask the question in testing health care interventions, as Haynes did:[16] Can it work? Does it work? Is it worth it?

Future directions

The importance of evidence-based medicine and the Cochrane Collaboration has become widely recognized by health professionals and lay people alike. Progress in applying these principles, as stressed most recently by Wijetunge and Baldock,[17] has been slow for a variety of reasons. First, hard evidence to support many treatments is simply not available because properly designed studies have not been performed. Second, the evidence may exist, but may not be easily accessible to those making the decisions. Third, even when available the evidence may not be accepted by those delivering care, particularly if it seems to be in conflict with perceived wisdom or personal experience, or if it threatens a vested interest.

We believe that the acceptance of evidence-based practice can be increased through the following strategies.

- By encouraging the use of evidence-based strategies in clinical practice and education.
- By learning to distinguish what we know from what we do not know.
- By focusing on clinically relevant outcomes.
- By directing our research efforts toward topics where evidence is non-existent or unclear.

Conclusions

If anaesthetists are to practice evidence-based medicine, the recommendations derived from the evidence must be widely accepted as the most authoritative statement that is currently available. This would involve an agreed strategy between the major research funding bodies and anaesthetic groups such as the American Society of Anesthesiologists (ASA), the European Society of Anaesthesiologists (ESA), the European Academy, the European Society of Intensive Care and the national societies. Anaesthetists are well known for cooperation and teamwork, and we are confident that this vision can become a reality. The size of the undertaking is considerable and the prospect daunting, but the potential benefits to us and our patients are great.

To register as a member of the Cochrane Anaesthesia Review Group, please contact our website www.cochrane-anaesthesia.suite.dk

References

1 Cochrane A. *Effectiveness and efficiency. Random reflections on Health Services. London.* Nuffield Provincial Hospitals Trust 1972.
2 Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; **312**: 71–2
3 Sackett DL, Richardson WS, Rosenberg WM, *et al.* Evidence-based medicine. *How to Practice and Teach Evidence-based Medicine.* Edinburgh: Churchill Livingstone, 1997
4 Evidence-based medicine. A new approach to teaching the practice of medicine. Evidence-Based Medicine Working Group. *JAMA* 1992, **268**: 2420–5
5 Woods D, Trewhellar K. Medline and Embase complement each other in literature searches. *Br J Med* 1998; **316**: 1166
6 Mulrow CD The medical review article: state of the science. *Ann Intern Med* 1987; **106**: 485–8
7 *The Cochrane Collaboration Handbook* Oxford: Update Software. Available in the Cochrane Library, 1999
8 Norman GR. Examining the assumptions of evidence-based medicine. *J Eval Clin Pract* 1999; **5**: 139–47
9 Charlton BG. Book review of evidence-based medicine. *J Eval Clin Pract* 1997: **3**: 169–73
10 Couto JS. Evidence-based medicine: a Kuhnian perspective of a transvestite non-theory. *J Eval Clin Pract* 1998; **4**: 267–75
11 Shahar E. A Popperian perspective of the term 'evidence-based medicine'. *J Eval Clin Pract* 1997; **3**: 109–16
12 Goodman NW. Who will challenge evidence-based medicine? *J R Coll Physicians Lond* 1999; **33**. 249–51
13 Goodman NW. Anaesthesia and evidence-based medicine. *Anaesthesia* 1998; **53**: 353–68
14 Horan BF. Evidence-based medicine and anaesthesia: uneasy bedfellows? *Anaesth Intensive Care* 1997; **25**: 679–85
15 Gøtzsche PC, Liberati A, Torri V, Rossetti L. Beware of surrogate outcome measures. *Int J Technol Assess Health Care* 1996; **12**: 238–46
16 Haynes B. Can it work? Does it work? Is it worth it? The testing of health care interventions is evolving. *BMJ* 1999; **319**: 652–3
17 Wijetunge A, Baldock GJ. Evidence-based intensive care medicine. *Anaesthesia* 1998; **53**· 419–21

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ABSTRACTS

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(The name of the presenting author is shown in bold type.)

Soluble adhesion molecules and endothelin in patients with fulminant hepatic failure: evidence for endothelial activation and injury

T. S. Walsh[1], S. J. Wigmore[2], A Lee[1] and J.A. Ross[2]

[1]University Departments of Anaesthetics and [2]Surgery, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW, UK

Fulminant hepatic failure (FHF) causes multiple organ dysfunction notably cardiovascular collapse, renal failure, and cerebral oedema. Endothelial–leucocyte interaction is implicated in the pathogenesis of organ dysfunction in the critically ill and is mediated via intercellular adhesion molecules. We have previously demonstrated early activation of circulating leucocytes in patients with FHF.[1] In this study we investigated endothelial activation by measuring circulating concentrations of endothelin and soluble selectins in patients with FHF.

We studied 14 patients with FHF (13 paracetamol-induced, 1 non-ABC hepatitis). All had grade III/IV encephalopathy, and were sedated, paralysed and mechanically ventilated. No patient had microbiological evidence of sepsis at the time of study. Arterial blood was centrifuged and stored at –70°C for subsequent analysis. Cardiovascular variables, oxygenation indices, prothrombin time, and multiple organ dysfunction scores (MODS) were recorded at the time of sampling. Analysis for soluble E, L, and P selectin and for endothelin-1 was by sandwich ELISA using commercial kits. All analyses were done in duplicate and concentrations averaged. For comparison venous blood was drawn from eight healthy volunteers.

Median prothrombin time in patients was 105 s (range 40–200). Seven patients fulfilled King's College criteria for poor prognosis of whom four died and three survived following liver transplantation. Of the remaining seven patients two died. The median MODS score was 12 (8–17). Concentrations of soluble selectins and endothelin are presented in Table 1. No relation was observed between selectin or endothelin concentration and cardiovascular parameters, oxygenation index, the presence of renal failure, norepinephrine requirement or survival. sL-selectin concentration correlated inversely with MODS (r=0.6, P<0.04).

Our data indicate significantly increased circulating concentrations of sE-selectin, sP-selectin and endothelin-1 in patients with FHF. These molecules originate primarily from endothelial cells and are released in response to activation or injury. Concentrations of sL-selectin, which is leucocyte-derived, were normal overall but correlated inversely with MODS score. This was interesting because sL-selectin concentrations have been inversely correlated with organ failure in at risk patients who develop ARDS.[2] We conclude that endothelial activation occurs in FHF.

Keywords: liver, intensive care

References

1 Wigmore SJ, Walsh TS, Lee A *et al. Intensive Care Med* 1998; **24**: 224–9
2 Donnelly SC, Haslett C, Dransfield I *et al. Lancet* 1994; **344**: 215–19

The effects of leucodepletion in patients with the Systemic Inflammatory Response Syndrome (SIRS)

M. Sabato[1], D F. Treacher[1], K A Brown[2] and V. Gant[2]

[1]Departments of Intensive Care and [2]Immunology, St Thomas' Hospital, London SE1 7EH, UK. [3]Department of Microbiology, UCLH, London WC1E 6DB, UK

Cardiopulmonary bypass may generate SIRS and subsequent multiple organ failure. Tissue damage is likely to arise from the untoward activity of infiltrating blood polymorphonuclear cells (PMNs) interacting with the endothelium of blood vessels to increase vascular permeability. The aim of this study was to determine the effect of leucodepletion in these patients, and to investigate whether leucofiltration of blood from SIRS patients modified the binding of PMNs to cultured endothelial cells.

Twenty-four patients who met SIRS criteria at 36 h after cardiac surgery were equally randomized to leucofiltration (LF) or control therapy. LF patients (nine male; APACHE II 21 ± 2; age 62 ± 10) received 1 h filtration cycles using a venovenous extracorporeal circuit at 200 ml min^{-1}, repeated at 12 h intervals. Control patients (12 male, APACHE II 21 ± 2; age 63 ± 9) received standard post-operative care. Hypoxaemia index (Pa_{O_2}/FI_{O_2}) was calculated up to 96 h from the onset of treatment. Blood from patients with SIRS was also subjected to leucofiltration in a laboratory-based

Table 1 Concentrations of circulating soluble selectins and endothelin-1 in patients with fulminant hepatic failure and in healthy controls. All values median (range). *P<0.04, **P<0.003, ***P<0.02 in comparison with healthy controls, Mann–Whitney U test

	sE-selectin ng ml^{-1}	sP-selectin ng ml^{-1}	sL-selectin ng ml^{-1}	Endothelin-1 ng ml^{-1}
Patients (n=14)	223 (143–317)*	184 (45–260)**	1421 (622–2501)	13 (1–39)***
Healthy controls (n = 8)	155 (116–190)	64 (18–108)	1321 (1027–2129)	3 (1–4)

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Table 2 SOFA scores at day 4 and day 7 compared to day 1. Mean (SEM) {interquartile range}

		Change from baseline SOFA score	
	SOFA score day 1	**At day 4**	**At day 7**
Dopexamine group	*n* = 52 9.4 (0.5) {3.7}	*n* = 39 –0.71 (0.5)	*n* = 28 –2.3 (0.7)
Control group	*n* = 48 10.3 (0.6) {5.2}	*n* = 45 –0.9 (0.5)	*n* = 29 –2.7 (0.6)

extracorporeal circuit and the PMNs examined for their ability to bind to monolayers of endothelial cells derived from human umbilical veins. The results are expressed as mean values ± SD.

Patients undergoing leucofiltration received an average 4.2 cycles (range 1–8). After 15 min the total leucocyte count fell from 16.2 ± 5.3 to 10.4 ± 3.3, the PMNs from 14.4 ± 5.2 to 8.3 ± 4.2, and platelets from 127 ± 87 to 117 ± 82×10^9 litre. All of the counts returned to baseline values by the end of the 60 min filtration period. The average length of stay for the LF and control group was 206 ± 118 and 214 ± 196 h respectively. Four LF patients and three control patients died before hospital discharge.

At 96 h, 2-way ANOVA showed that the hypoxaemia index was significantly improved in the LF group compared with control patients ($P<0.001$). Haemofiltration was required in three control patients, but none of the LF group. No complications relating to leucofiltration occurred during the study. The *in vitro* leucofiltration of SIRS blood produced 60% reduction ($P<0.001$) in the number of PMNs adhering to endothelial monolayers.

In conclusion, the present study demonstrates that leucofiltration safely removes circulating PMNs from patients with SIRS following cardiopulmonary bypass. The removal from SIRS blood of PMNs that adhere to endothelium could reduce the sequelae of events that underlie organ failure in this disorder, particularly as lung function of SIRS patients is improved by leucofiltration treatment.

Keywords: intensive care; complications, organ failure

The effect of dopexamine on organ dysfunction in the critically ill patient

C. Ralph[1], S J Tanser[1], P Nelms[1], D G. Sinclair[2] and
P D Macnaughton[1]

[1]*Intensive Care Units Derriford Hospital, Plymouth PL6 8DH, UK.*
[2]*Torbay Hospital, Torquay TQ2 7AA, UK*

It has been postulated that an increase in gut hyperpermeability may be an important factor in the development of multiple organ failure and mortality in the critically ill.[1] Dopexamine increases splanchnic blood flow and has been shown to maintain gastrointestinal integrity by reducing hyperpermeability in certain groups of critically ill patients.[2] We have assessed the effect of a prolonged infusion of dopexamine in preventing multiple organ failure in a randomised controlled study. Organ dysfunction was quantified by the SOFA (sequential organ failure assessment) score.[3]

After initial resuscitation, critically ill patients predicted to require organ support in intensive care for more than 4 days were randomly allocated to receive dopexamine at 2 $\mu g\ kg^{-1}\ min^{-1}$ as an infusion for 7 days or control. SOFA scores were performed daily throughout the study period using the most abnormal value for each parameter in each 24-h period.

One hundred patients were recruited to the study, of whom 52 received dopexamine. There was no significant difference in ages (mean (SD): dopexamine 62 yr (15.6); control 58 yr (18)), APACHE scores (dopexamine 20.9 (6.6); control 20.2 (5.9)), length of stay (dopexamine 9.7 days (1.08); control 12 days (0.94)), or survival to hospital discharge (dopexamine 23/52; control 22/48). We tested for a difference in SOFA scores at day 4 and day 7 compared to day 1 (Table 2).

Table 3

		Control	Shock 0 min	Shock 30 min	Reinfusion
MAP (mmHg)	H	78	44	53	88
	HNS	98	84	76	113
SVR (dyn s cm^{-5} kg)	H	45146	45200	51571	47736
	HNS	44051	74441	67220	45200
GBF (normalized %)	H	100	60	74	98
	HNS	100	45	46	92
Lactate (mmol $litre^{-1}$)	H	1.8	2.3	2.4	2.3
	HNS	1.4	3.3	4.5	4.8

We conclude that in this group of critically ill patients a prolonged infusion of dopexamine did not have any beneficial effects in terms of mortality, length of ICU stay or organ failure score.

Keywords: complications, organ failure

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References

1 Doig CJ *et al. Am J Respir Crit Care Med* 1998, **158**: 444–51
2 Sinclair D *et al. Intensive Care Medicine* 1997; **23**: 510–16
3 Vincent JL *et al. Crit Care Med* 1998; **26**: 1793–800

Injury abolishes the spontaneous haemodynamic recovery from simple haemorrhage

B. A. Foëx, T. Rainey and R. A. Little

North Western Injury Research Centre, University of Manchester,
Stopford Building. Oxford Road, Manchester M13 9PT, UK

Blunt trauma can be regarded as a combination of haemorrhage and tissue injury. The haemodynamic response to haemorrhage is well known. We wanted to examine the effect of injury on aspects of the haemodynamic and metabolic response to haemorrhage.

Young Large White pigs, anaesthetised with alphaxalone/alphadolone (15 $mg\ kg^{-1}\ h^{-1}$), were subjected to a haemorrhage of 30% of their total blood volume, with or without a background of brachial nerve afferent nociceptive stimulation (NS) to mimic injury Shed blood was re-infused after a 30-min shock period. Haemodynamic, gut blood flow (GBF), and plasma lactate measurements were made and oxygen transport variables calculated and analysed using repeated measures ANOVA (Table 3).

Haemorrhage (H) resulted in: (i) a tachycardia, (ii) hypotension, which recovered during the shock phase, (iii) a reduction in gut blood flow, which recovered during the shock phase, but, (iv) no increase in plasma lactate concentration. Nerve stimulation resulted in the expected 'pressor response' of tachycardia and increased blood pressure. Trauma, modelled using haemorrhage with nerve stimulation (HNS), differed haemodynamically and metabolically from haemorrhage alone: there was, (i) no recovery of mean arterial pressure (MAP) during the shock phase ($P<0.0001$), (ii) an immediate increase in systemic vascular resistance (SVR), (iii) a greater reduction in gut blood flow ($P=0.012$), (iv) gut vasoconstriction ($P<0.0001$), and (v) increased plasma lactate ($P=0.043$). Global oxygen consumption was unchanged despite a reduction in oxygen delivery with haemorrhage and nerve stimulation. The oxygen extraction ratio increased in the haemorrhage and the haemorrhage plus nerve stimulation groups, but this did not compensate for the greater metabolic insult provided by haemorrhage plus nerve stimulation compared with haemorrhage alone.

So, the combination of haemorrhage plus injury (mimicked by afferent nociceptive stimulation) results in greater haemodynamic and metabolic disruption than haemorrhage alone. This needs to be considered in the development of better treatments for blunt trauma patients.

Keywords: complications, haemorrhage; pig

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Indomethacin: its role in the management of intractable intracranial pressure (ICP) after severe head injury

J. S. Bewley, A. E. R. Young and A. R. Manara

The Intensive Care Unit, Frenchay Hospital, Frenchay Park Road, Bristol BS16 1LE, UK

Intracranial hypertension that fails to respond to first line medical and surgical treatment after head injury is associated with a 92% mortality overall.[1] The addition of barbiturates will result in a good or moderate neurological outcome in 35% of patients,[2] but those with hyperaemia do significantly worse. However barbiturates may not be a logical choice for those patients whose intracranial hypertension is secondary to hyperaemia, and may be associated with significant complications. In these patients cerebral vasoconstrictors such as indomethacin may be more appropriate and possibly associated with fewer unwanted effects. In one study six out of 10 patients who received indomethacin for intracranial hypertension unresponsive to barbiturates survived.[3] However it is unclear how many were hyperaemic since jugular venous saturation ($S\mathrm{j}_{O_2}$) was not monitored. We report our experience with indomethacin in 10 severely head-injured patients.

Our protocol aims to maintain a target cerebral perfusion pressure (CPP) and ICP through the application of sedation, diuretics, CSF drainage, mild hypothermia, muscle relaxation and control of arterial carbon dioxide (Pa_{CO_2}). If the ICP remains elevated then $S\mathrm{j}_{O_2}$ is monitored. The combination of raised ICP and $S\mathrm{j}_{O_2}$ is taken to indicate hyperaemia (absolute or relative). In these circumstances the patient is hyperventilated to a Pa_{CO_2} of 28 mmHg and if necessary an intravenous infusion of thiopentone commenced. We used indomethacin infusions in 10 patients fulfilling these criteria of hyperaemia. In seven patients the hyperaemia was confirmed as absolute by demonstrating a raised middle cerebral artery velocity (MCAV) with transcranial Doppler. The mean age of the patients was 21.2 yr (range 8–55). Indomethacin was infused for a mean of 3.8 days (1–11) at a rate of 3–11 mg h^{-1}. The effect of indomethacin on mean (SD) ICP, CPP and $S\mathrm{j}_{O_2}$ is shown in Table 4.

Table 4

	ICP (mmHg)	CPP (mmHg)	$S\mathrm{j}_{O_2}$ (%)	Pa_{CO_2} (mmHg)
Before indomethacin	29.4 (8.14)	71.5 (6.87)	81.4 (3.63)	29.2 (3.22)
After indomethacin	14.6 (6.38)	84.7 (11.5)	69.2 (6.12)	29.6 (3.06)
P value	0.00025	0.017	0.000069	0.49

Table 5

Withdrawal rate *vs* bed occupancy	Cross correlation	Standard error	Significance
3/96–2/99	0.042	0.030	$P = 0.162$

At 6-month follow up there were seven survivors (three good recovery, three moderate recovery, one severely disabled). Three patients died with intractable ICP and septic shock. Two of these patients had associated renal failure. There were no episodes of gastrointestinal bleeding. Two of the three patients who died did not have MCAV measured, and therefore indomethacin may not have been strictly indicated. These results achieved in this subgroup of head injured patients is much better than that expected, and matches the outcome achieved in the overall ICU head injury population. Indomethacin may have a role in the management of raised ICP associated with hyperaemia after severe head injury. We recommend however that it should only be used with monitoring of both $S\mathrm{j}_{O_2}$ and MCAV.

Keywords: intensive care, head injury

References

1 Miller JD, Butterworth JF, Gudeman SK, *et al J Neurosurg* 1981; **54**: 289–99

2 Kelly DF, Kordestani RK, Martin NA, *et al. J Neurosurg* 1996; **85**: 762–71

3 Biestro AA, Alberti RA, Soca AE, *et al J Neurosurg* 1995; **83**. 627–30

The influence of intensive care unit (ICU) workload on decisions to withdraw treatment

J. S. Bewley[1], F E. M. Braddon[2], K Waters[2] and A. R. Manara[1]

[1]*Intensive Care Unit and* [2]*Research and Development Support Unit, Frenchay Hospital, Frenchay Park Road, Bristol BS16 1LE, UK*

The incidence of treatment withdrawal is increasing across Europe and the UK, a recent report from this unit showing that treatment is withdrawn in 12.5% of patients admitted to ICU and accounts for 60% of all deaths in the ICU.[1] Nationally, data from the Intensive Care National Audit and Research Centre (ICNARC) report a withdrawal rate of 11.8%, accounting for over 50% of all deaths in intensive care.[2] The effect of workload on treatment withdrawal has not been specifically examined previously, although data from ICNARC suggest that treatment is withdrawn from an increased proportion of ICU patients in the winter months when the pressure on ICU facilities is known to be greatest.[2]

We have collected data on treatment withdrawal prospectively for the 3-yr period March 1996 – February 1999. During this time 1574 patients were admitted to ICU and treatment was withdrawn in 200 (12.7%) patients. The daily rate of treatment withdrawal was correlated with the daily bed occupancy over this period. The time (in hours) from admission to ICU until the decision to withdraw treatment was made, was calculated. This was then correlated with the number of patients admitted to ICU on the day that treatment was withdrawn (Tables 5 and 6).

These data suggest that an increase in ICU workload does not

Table 6 *Spearman's rank test P=0 043

No. of patients admitted daily	No. of patients having treatment withdrawn	Hours from admission to treatment withdrawal decision (median, interquartile range)
0	21	81 (42–154)*
1–2	135	33 (10–75)*
3 or more	44	21 (7–93)*

increase the frequency with which treatment is withdrawn, but that it does however result in the decision to withdraw treatment being made earlier in the course of the patient's ICU stay. It is essential to ensure that the decision-making and its timing are as appropriate when ICU facilities are under pressure as when they are not. Further analysis of ICNARC data is necessary to determine if workload is a factor influencing the decision nationally.

Keywords: intensive care, audit

References

1 Manara AR, Pittman JAL, Braddon FEM. *Anaesthesia* 1998; **53**: 523–8

2 Intensive Care National Audit and Research Centre Case Mix Programme Database

MRSA: predictor of outcome in critically ill patients

C. P. Subbe[1], G G Rao[1], P. Sedgwick[2], N. Van Heerden[1] and C. B Groba[1]

[1]*Intensive Care Unit and Department of Microbiology, University Hospital Lewisham, Lewisham SE13 6LH, UK.* [2]*Department of Public Health Sciences, St. George's Hospital Medical School, Tooting SW17 0RE, UK*

Methicillin resistant *Staphylococcus aureus* (MRSA) infection in critically ill patients is associated with considerable morbidity, mortality and cost.[1 2] In 1994, we studied 29 MRSA positive patients admitted to the intensive care unit (ICU). Although the size of population studied was too small to be conclusive, there was a suggestion that MRSA did not have a significant impact on overall mortality (unpublished observation), however, there was an increase in average length of stay.

In this retrospective study, microbiology records identified MRSA infected/colonised patients admitted to ICU over 36 months (1996–1998). Patient demographics, site of isolation and hospital mortality were recorded. Isolation of MRSA from blood, sterile sites or endotracheal secretions was considered to be a surrogate marker of serious infection. In those patients with MRSA isolated in multiple sites, the most likely site for serious infection was selected

One hundred and sixty seven patients were found to be infected/colonized with MRSA and of these 59 patients had positive blood or sputum cultures. Hospital mortality of MRSA positive patients was 50.9% compared to 33.8% overall hospital mortality of all ICU patients. Standardized incidence ratio for death was 1.51 (95% confidence interval 1.20–1.86) for patients with MRSA. As expected the number of deaths rises with age (≤60 yr was 34.8%, 61–75 yr 52.6%, >75 yr 64.4%. Odds ratio 2.74 (95% confidence interval 1 09–6.93) for >75 compared with ≤60 yr old).

Diagnosis of MRSA from blood and sputum (group A) had a mortality of 44.1%, compared to 51.3% in those with MRSA from screening sites (group B) (P=0.403). Whilst mortality increases with age for both groups, it rises faster in patients with MRSA in group B (Table 7).

There was no difference in mortality between groups. The poor association between mortality and positive blood or sputum cultures corroborates our previous observation that detection of MRSA is more likely to be an indicator of poor prognosis rather than the cause of fatal infection.

Table 7 MRSA from significant sites (Group A) *vs* screening sites (Group B) *Number of patients in each group

Age	≤60 yr (40)*		61–75 yr (58)*		75 yr (37)†	
	Group A	Group B	Group A	Group B	Group A	Group B
Survival	58 8%	69 6%	57.7%	43.8%	50.0%	33 3%
Mortality	41.2%	30.4%	42.3%	56.2%	50 0%	66.7%

Keywords: intensive care, audit

References

1 Romero-Vivas G, Rublo M, Fernandez C, Picazo JJ. *Clin Infect Dis* 1994; **32**: 25–30

2 Harbarth S, Rutschmann O, Sudre P, Pittet D *Arch Intern Med* 1998; **158**: 182–9

A prospective study to assess the demand for a high dependency unit (HDU) in a district general hospital based on the guidelines issued by Department of Health (DoH) (NHS Executive) 1996[1]

S. P. L. Meghjee and R J. T. Wilson

York District Hospital, Wigginton Road, York YO31 8HE, UK

A challenge for doctors is to identify, at an early stage, which patients are most likely to benefit from HDU care [1 2] The NHS Executive (1996) have set guidelines[1] to define the main issues to be considered when deciding which patients need HDU care.

York District Hospital (YDH) has 838 beds serving a catchment area of approximately 300 000 people. Facilities for an ICU of six beds with no HDU beds or five ICU beds with two HDU beds is provided.

Over a period of 20 days (three random and 17 consecutive days) the main surgical and medical wards (total of five wards) were visited daily by one medical investigator identifying patients who might have been considered for admission to HDU, had it been available. The following data were recorded.

(a) Date that the patient first fulfilled the criteria for HDU admission.
(b) Details of the organ system that required support.
(c) Date that HDU was no longer considered necessary. (This may have been due to patient getting clinically better or worsened requiring either a formal admission to HDU or ICU, or death.)
(d) Details of patient transfers to other wards or departments, including ICU or other specialist units in nearby hospitals.

The two HDU beds were also monitored consecutively for 38 days and the same data were collected. The other medical and surgical wards (17 wards) were not audited, except the number of admission from them into either HDU or ICU.

There were 1327 admissions into the adult medical and surgical specialities, of which 687 were elective and 640 emergency admissions. The audited wards had 287 (45%) emergency and 60 (11%) elective admissions Seventeen patients (six surgical and 11 medical) were identified to qualify for HDU. Out of the 11 medical patients, two (18%) patients were admitted to ICU, of whom one (9%) died. Nine (82%) patients improved. Their mean HDU stay was 3 days. In the surgical audited wards, six patients were identified of whom one (17%) was admitted to ICU. The other 5 (33%) got better and were discharged. Their mean HDU stay was 3.6 days. Two surgical patients, despite being clinically very ill, did not meet any categories in the NHS guidelines. Both patients were admitted to ICU of whom one died. Reviewing their notes, the outstanding biochemical abnormality was presence of severe metabolic acidosis Five patients were admitted to ICU from the non-audited wards (total 17 wards with 353 (55%) emergency and 627 (89%) elective admissions during the study period). Twenty-seven patients were admitted to the existing HDU in 38 days. These were from theatre (62%), casualty (10%), wards (14%) and from ICU (14%). Four (14%) patients were transferred to ICU, of whom one (3%) died.

From the above data, it was predicted that a six bed HDU would be occupied to full capacity for 100% of the time. The guidelines are self explanatory and easy to follow, and therefore should be easily implemented. To increase the specificity of the guidelines, we recommend addition of severe acid base disorders to the guidelines.

Keywords: intensive care unit, audit

References

1 Guidelines on admission to and discharge from Intensive Care and High Dependency Units: NHS Executive; Department of Health 1996

2 McQuillan P, Pilkington S, Allan A, et al *BMJ* 1998; **316:** 1853–7

3 National Confidential Enquiry into Perioperative Deaths, 1993

Prospective evaluation of a modified Early Warning Score to aid earlier detection of patients developing critical illness on a general surgical ward

C. Stenhouse, S Coates, M Tivey, P. Allsop and T. Parker

Intensive Care Department, Queen's Hospital, Burton Hospitals NHS Trust, Belvedere Road, Burton on Trent, Staffordshire DE13 0RB, UK

Admissions to the intensive care unit (ICU) from the wards have a higher mortality when compared to patients admitted from the operating theatres/recovery and accident and emergency department.[1] Suboptimal care may contribute to morbidity and mortality of patients admitted from the ward.[2] Failure to appreciate physiological derangements of breathing and mental status has been demonstrated in patients who subsequently suffered cardiac arrest, and these events may have been apparent up to 8 h prior to the event.[3] [4] The Early Warning Score (EWS) was developed as a simple scoring system to be used at ward level utilising routine observations taken by nursing staff.[5] Deviations from the normal score points and a total is calculated.

The EWS was evaluated prospectively for 1 month. The score was then modified to include urine output, to make temperature deviations less sensitive and to include normalised blood pressure (Table 8). We then evaluated this prospectively for 9 months.

A total score of 4 or more resulted in the patient being reviewed by ward medical staff and help sought from the intensive care team if appropriate. Over a 9-month period 206 patients on two general surgical wards were put on the scoring system, of these 26 were admitted to the ICU. The APACHE II scores of these patients was 16.6 (± 7.3). Eleven patients were admitted to the ICU from the surgical ward who had not been monitored on the modified EWS and their admission APACHE II scores were 23.5 (± 4.1). This compares with admission APACHE II scores of 22.3 (± 5.5) in 43 patients admitted from surgical wards in the 9-month period prior to introduction of the system The introduction of the system has appeared to lead to earlier referral to the intensive care unit

Keywords: intensive care, audit

References

1 Goldhill DR, Sumner A *Crit Care Med* 1998, **26.** 1337–45

2 McQuillan P, Pilkington S, Allan A *et al. BMJ* 1998; **316.** 1853–8

3 Franklin C, Mathew J. *Crit Care Med* 1994, **22:** 244–7

4 Schein RM, Hazday N, Pena M *et al Chest* 1990, **98** 1388–92

5 Morgan RJM, Williams F, Wright MM. *Clin Intensive Care* 1997, **8.** 100

Outcome in patients with acute respiratory distress syndrome transferred to a tertiary referral centre

R. Marshall, S Webb and G. Bellingan

Nowle Centre for Respiratory Research, University College London, 5 University Street, London WC1E 6JJ, UK

ARDS represents a severe and rapid form of acute lung injury that continues to be associated with a high mortality rate of between 40 and 70%. Approximately 1500 cases occur each year in the UK and although ARDS contributes significantly to the demands made on ITU resources, an individual unit may only expect to see a handful of cases each year. Recent guidelines published by the Intensive Care Society outline 'best practice' for the safe transfer of such individuals however the potential risks/benefits of transfer to a tertiary referral centre remain unclear. In particular, it is not known whether the referral of patients later in the course of ARDS might result in a significantly worse outcome University College Hospitals Intensive Care Unit has a Mobile Intensive Care Ambulance available on a 24 h basis for the retrieval of critically ill patients. We have prospectively examined the hospital and ICU mortality for ARDS patients transferred to our centre. All patients admitted to the ICU fulfilling ERS/ATS

Table 8

Score	3	2	1	0	1	2	3
HR		<40	40–50	51–100	101–110	111–129	⩾130
RR		⩽8		9–14	15–20	21–29	⩾30
Temp		<35.0		35.0–38.4		⩾38.5	
CNS				Alert	Voice	Pain	Unresp
Urine output	Nil	<1 ml kg^{-1} 2 h^{-1}	<1 ml kg^{-1} h^{-1}		>3 ml kg 2 h^{-1}		
Systolic BP	>45%↓	30%↓	15%↓	Normal for patient	15%↑	30%↑	>45%↑

Table 9 Values represent mean (SD). *P* values represent results of Student's *t*-test except *chi-squared test

	Transferred group	In-hospital group	*P* value
Age (years)	48 (22–78)	50 (18–77)	0 66
APACHE II score	20 (7)	21 (7)	0.8
SAPS 2 score	37 (15)	33 (22)	0 26
ICU mortality	39.6%	31 0%	0 064*
Hospital mortality	47.9%	34 5%	0 00047*
Days after diagnosis on admission	1.9 (8 9)	−2 9 (4.4)	0.013

consensus criteria for ARDS were identified over a period of 21 months. Clinical and demographic data were recorded onto a computerized database. ICU and hospital mortality were also recorded for all patients, including those subsequently transferred back to their referring hospital.

A total of 77 patients were identified. Table 9 summarizes the admission and outcome data. Overall ICU and hospital mortality was 36.4% and 42.8% respectively, and compares favourably with published series. 62 3% of all ARDS patients were transferred from outside hospitals at an average of 1.9 days after the diagnosis of ARDS. No significant complications occurred during transfer. There were no significant differences in admission severity scoring (APACHE II or SAPS 2 criteria) or in baseline demographics between the transferred and 'in-hospital' groups. There was no difference in ICU mortality between the groups however hospital mortality was higher in the transferred patients (84% of patients leaving the ICU were transferred directly back to their referring hospital). In conclusion, the ICU mortality for patients transferred with ARDS in this series was no greater than an in-hospital cohort, despite admission at a later time after diagnosis. The transfer of patients with ARDS should be considered potentially safe and may be appropriate for the purposes of accessing specific clinical resources or involvement in therapeutic trials.

Keywords: intensive care, audit

Intensive care for severe falciparum malaria; a retrospective study of clinical course and outcome of 53 cases managed in a London teaching hospital

S. Webb[1], M. Evans[2], S. Batson[1], R Jennings[2], D. Mabey[2], A Webb[1] and G. Bellingan[1]

[1]*Intensive Care Unit (ICU) and* [2]*Hospital for Tropical Diseases (HTD), University College London Hospitals (UCLH), Mortimer Street, London W1N 8AA, UK*

Imported falciparum malaria is increasing in incidence in the UK and carries a mortality of 0.7%.[1] A total of 53 patients were admitted to the UCLH ICU between January 1994 and August 1999, 13 in the 36 months January 1994 and December 1996 and 40 in the 31 months January 1997 to date.

Results are shown in Table 10. Mechanical ventilation was required for 8.5 (SD 7.4) days and haemofiltration for 9.2 (6.8) days. All six patients who died were mechanically ventilated and haemofiltered. Survival in those who required both ventilation and haemofiltration was 8/14 (57%), this increased to 68% for ventilation alone and 71% for haemofiltration alone.

Table 10 Data are presented as mean (SD). Student's *t*-test and Fisher's Exact tests were used as appropriate Parasitaemia is defined as the parasite count on admission to the ICU, thrombocytopenia as a platelet count of $<20\times10^9$ litre^{-1}, cerebral dysfunction as a reduction in Glasgow coma score or fits, and renal and pulmonary dysfunction as the requirement for haemofiltration or mechanical ventilation

Patients	Total	Pre 01/01/97	Post 01/01/97	*P*
Age	45 (17–23)	39 (24–62)	47 (17–83)	NS
APACHE II	18 (9)	23 (11)	16 (7)	0.013
% Parasitaemia	13 (13)	20 (13)	11 (12)	NS
Deaths	6/53 (11%)	5/13 (38%)	1/40 (3%)	0 002
Organ dysfunction				
Thrombocytopenia	18/38 (47%)	No data	18/38 (47%)	
Renal	19/53 (36%)	8/13 (62%)	11/40 (28%)	0.044
Pulmonary	19/53 (36%)	8/13 (62%)	11/40 (28%)	0 044
Cerebral	18/53 (34%)	4/13 (31%)	14/40 (35%)	NS

This report describes the largest cohort of imported falciparum malaria in adults requiring intensive care in the western world The number of ICU admissions increased significantly after 1996 and the mortality fell dramatically This was associated with a reduction in severity of illness (significantly lower APACHE II score, mean parasite count and reduction in organ support) but a greater fall in the standardised mortality ratio (SMR). APACHE II mortality prediction fell from 62 to 28% and the SMR from 0.95 to 0.08, suggesting outcome may have improved. The reasons for the significant increase in admissions include a slight increase in imported malaria in the UK (a mean of 1191 per annum cases over 1994–96 to 1370 per annum cases 1997–98).[1] However, earlier referral, greater awareness and close collaboration between referring hospitals, HTD and our ICU must account for most of this altered practice. Reasons for the reduction in mortality include: (i) Earlier referral of patients before they become critically unwell. (ii) Referral of patients for high dependency care. (iii) Altered pattern of care in ICU — prior to 1997 there was a tendency to restrict fluid in severe malaria and only admit patients with severe organ failure. More recently, practice has changed with earlier admission. careful haemodynamic monitoring and avoidance of hypovolaemia. (iv) Greater use of exchange transfusion. (v) Expertise may have improved as a result of increased case exposure.

Reference

1 Figures kindly supplied by the Malaria Reference Laboratory, London School of Hygiene and Tropical Medicine, London, UK

Effect of pro- and anti-inflammatory agents on the clearance of macrophages from the inflamed peritoneal cavity

F. Chua[2], H. Cooksley[2], S. Mutsaers[2], G. Laurent[2] and G Bellingan[1]

[1]*Bloomsbury Institute of Intensive Care and* [2]*Centre for Respiratory Research, Rayne Institute, London WC1E 6JJ, UK*

Macrophages are cleared from the inflamed peritoneal cavity by active emigration through the mesothelial lining to the draining lymph nodes and this represents a key aspect of the resolution of the inflammatory response. We have previously shown in murine models that the clearance of inflammatory macrophages from resolving acute peritonitis is rapid (half-life <2 days) compared with resident macrophages from the non-inflamed peritoneum (half-life >14 days). The mechanisms which control the differences in these rates of clearance are unknown but we hypothesized that macrophage adhesion interactions may regulate inflammatory cell clearance.

To determine if macrophage adhesion altered during the course of peritonitis we examined the ability of macrophages lavaged at different times over the course of acute peritonitis to adhere to mesothelial cells *in vitro* In our murine model of acute peritonitis — i.p. 4% Brewers thioglycollate (TG), macrophage numbers were shown to peak within the peritoneum at day 5 after challenge and decline to control levels by day 10 through to day 14. Inflammatory cells (>92% macrophages) were collected at 5–14 days after challenge, fluorescently labelled with the cell tracking dye CMFDA, and added in equal numbers (1×10^5 cells well^{-1}) to confluent monolayers of mesothelial cells (transformed mesothelial cell line — Met5A) in 96 well culture plates. After 45 min adhesion, non-adherent cells were washed off and the number of adhered cells determined using a fluorescent plate reader. With adhesion of non-inflamed resident macrophages taken as control, the macrophage population lavaged 5 days after TG challenge exhibited a 31 (3.4)% (mean (SD)) greater adhesion to the mesothelial layer than controls, this had decreased to 26 (5.2)% less than controls by day 14 ($P<0.05$, $n=10$) demonstrating that macrophage-mesothelial adhesion was under dynamic control over the course of peritonitis. To determine if clearance could be altered *in vivo* we fluorescently labelled day 5 macrophages *in vivo* by intra-peritoneal (i.p.) injection of the fluorescent label PKH26-PCL prior to exposure to either i.p *Escherichia coli* LPS (50 µg animal^{-1} $n=7$) or i.p. methylprednisolone (1 mg animal^{-1} $n=5$) as pro- and anti-inflammatory agents respectively. Controls were injected with the same volume of water i.p. ($n=7$). All mice were sacrificed 4 days later and the number and per cent inflammatory macrophages remaining in the peritoneal cavity determined by flow cytometry. Compared with controls LPS induced a 72 (12)% reduction and methylprednisolone induced a 23 (8)% increase in the percent fluorescently labelled macrophages recovered ($P<0.05$). The total number of macrophages (fluorescently labelled and non-labelled newly labelled macrophages) recovered was similar in all three groups suggesting that altering the activation state can significantly increase or decrease the cycling of macrophages through the peritoneal cavity. The effects of these alterations on the resolution of inflammation await elucidation.

Keywords: peritoneal cavity, macrophages; mouse

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The detection of circulating endothelial cells in human septic shock

M. Mutunga, A. Gascoigne, A Batchelor, R. Bullock, B Fulton, J Gillespie and **S. V. Baudouin**

University Department of Surgical and Reproductive Sciences and the Department of Anaesthesia and Intensive Care, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, UK

The vascular endothelium has a central role in the control of microvascular tone and it has been hypothesized that vascular endothelial damage occurs in septic shock, producing multi-organ failure.[1] Isolated endothelial cells (EC) exposed to pro-inflammatory cytokines and other mediators upregulate surface adhesion molecules, synthesize vasoactive compounds and express pro-coagulant factors. However, there is little direct evidence of EC damage in human sepsis due to the inaccessibility of the vascular endothelium. Circulating EC have been detected in a number of vascular diseases including coronary artery and sickle cell disease. We therefore hypothesized that circulating EC would be detectable in septic shock.

Cell seeding experiments were initially performed to validate the isolation method. Known concentrations of human umbilical endothelial cells (HUVECS) were seeded into whole blood and recovered by an isopycnic centrifugation method using Percoll suspension. EC were identified using antibodies to Factor VIII and the vascular endothelial growth factor receptor, KDR by an indirect immunofluorescence technique using FITC and PE-conjugated secondary antibodies. EC were counted using an inverted fluorescence microscope and expressed as recovered cells per ml of blood. A recovery rate of over 90% was achieved with cell concentration between 50 and 100 cells ml^{-1}. At a dilution of 10 cells ml^{-1} recovery fell to less than 40%. Non-specific binding was assessed using isotype control antibodies and subtracted from the final count.

Table 11 Numbers of circulating endothelial cells ml^{-1} of blood (SEM)

	Controls (n = 11)	ITU controls (n = 9)	Septic patients (n = 15)
Factor VIII +ve cells	1.9 (0.5)	2.6 (0.6)	30.1 (3.3)
KDR +ve cells	0.7 (0.3)	0.5 (0.2)	10.4 (1.2)

Blood samples were taken from freshly placed and flushed venous lines from 11 healthy volunteers, nine ventilated ICU control patients without sepsis and 15 patients with septic shock The cells were separated, identified and counted as described above. Cell counts using the Factor VIII antibody were consistently higher than those using KDR but correlation between the two counts was high ($r=0.98$) (Table 11).

There was a significant increase in circulating EC, identified with both Factor VIII and KDR, in patients with septic shock, compared to both healthy volunteers and ICU controls ($P<0.001$; ANOVA). EC were also successfully cultured from seven patients with sepsis. Circulating EC can be identified and isolated during septic shock. This suggests that endothelial disruption is occurring in human sepsis.

Keywords: complications, septic shock

Acknowledgement

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Reference

1 Parrillo JE. *New Engl J Med* 1993, **328**: 1471–7

Evaluation of the Oxford protocol for total spinal clearance in the unconscious trauma patient

R. A. Brooks and K. M Willett

Department of Trauma, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 DDU, UK

Background: All patients admitted to an intensive care unit following significant blunt trauma must be assumed to have a spinal fracture until proved otherwise. Plain radiology alone is not reliable in excluding a fracture of the cervical spine and there is controversy regarding the investigations required to clear the spine in the unconscious patient.[1 2] Prolonged immobilization of the spine enforces a recumbent position and is associated with significant morbidity including occipital and mental pressure sores and reduced cerebral perfusion pressure.[3] A protocol has been developed at the Trauma Unit of the John Radcliffe Hospital to enable safe and early discontinuation of spinal immobilization in the unconscious trauma patient.

Methods and results: Assessment of the spine in the unconscious multiply injured patient at the Trauma Service at the John Radcliffe Hospital, Oxford, since April 1994 includes plain anteroposterior and lateral radiographs of the whole length of the spine, CT scanning of C1 and C2 and dynamic flexion and extension screening of the cervical spine under fluoroscopic control.

The results of this policy over a 3.5 yr period in 216 consecutive patients admitted to the intensive care unit were reviewed.

Forty-one patients had a spinal fracture. Nineteen patients had a fracture at more than one level and these were non-contiguous in nine patients. The diagnosis of spinal fracture was made prior to extubation in all but two patients who died before investigations were completed. Three patients developed occipital pressure sores relating to prolonged use of a rigid cervical collar.

Seventy-eight patients underwent dynamic screening of the cervical spine. Five of these patients had a cervical fracture or instability. Three had been identified on plain radiography but screening was used to determine stability. In another patient, a stable spinous process fracture became visible on screening. The fifth patient demonstrated minor changes on plain radiography but gross instability on dynamic screening. There were no neurological sequelae in these or any other patients. Collar removal was therefore possible in all but one patient a median 3 days prior to extubation and one day after admission to ICU.

Conclusion: In our limited study a full length spinal radiography protocol with CT scanning of C1 and C2 and dynamic screening of the cervical spine allows early and safe discontinuation of spinal precautions to facilitate nursing care and minimise complications in the unconscious patient.

Keywords. complications, coma; complications, trauma

References

1 Gupta KJ, Clancy M *BMJ* 1997; **314**: 1652–4

2 Lockey AS, Handley R, Willett K. *Injury* 1998; **29**: 493–7

3 Raphael JH, Chotai R. *Anaesthesia* 1994; **49**: 437–9

The characteristics of patients given antidepressants while recovering from critical illness

C. Jones[1], P. Skirrow[1], R D Griffiths[1], G Humphris[2], S. Dawson[3] and J Eddleston[3]

[1]*Intensive Care Unit, Whiston Hospital, Prescot L35 5DR and Department of Medicine, University of Liverpool, L69 3GA, UK* [2]*Department of Clinical Psychology, University of Liverpool, L69 3BX, UK.* [3]*Intensive Care Unit, Manchester Royal Infirmary, Manchester M13 9WL, UK*

Antidepressants are occasionally given to recovering intensive care (ICU) patients, either while in ICU, or shortly afterwards on the ward. However there is little research on what characterizes these patients or their longer term psychological recovery. As part of a larger rehabilitation study data were collected on the characteristics of ICU patients receiving antidepressants while in hospital and their progress up to 6 months post ICU.

Recovering ICU patients were approached once it was clear the patient was expected to survive to 6 months. A record was made of antidepressant medication and depression was assessed using the Hospital Anxiety and Depression Scale (HAD). Psychological recovery was assessed at 2 and 6 months post ICU using the HAD[1] and the Fear questionnaire[2] to record panic attacks/phobias and physical recovery was similarly recorded using the SF-36.

Seventy-six patients completed the HAD at 2 weeks, 2 months and 6 months post ICU. All the patients had been intubated and had had an ICU stay $\geqslant$48 h, 18 had received antidepressants either in the ICU or shortly afterwards on the ward for a clinical diagnosis of depression. Patients receiving antidepressants were much more likely to have had a longer ICU stay and a longer hospital stay (see Table 12).

The fear questionnaire scores were not related directly to the length of ICU stay. The questionnaire allows the examination of which particular areas patients are having difficulty with. Patients receiving antidepressants were becoming panicky travelling alone, being alone in a busy street or far from home, and going shopping alone.

The data suggest that the use of antidepressants at times may be inappropriate. The difficulty of establishing the diagnosis of depression in ICU may mean that only soft clinical criteria are used. This is more likely to occur in longer stay patients. Passivity due to a learned helplessness state may be diagnosed as depression while patients are intubated. This would fit with these patients having difficulty performing activities alone. Alternatively a subdued anxiety state may be similarly being misdiagnosed as depression.

Keywords: ataractics, antidepressants; intensive care, audit

References

1 Zigmond AS, Snith RP. The Hospital Anxiety and Depression Scale. *Acta Psych Scand* 1983; **67**: 361–70.

2 Marks IM, Matthews AM. Brief standard self-rating scale for phobic patients. *Behav Res Ther* 1979; **17**: 263–7.

Predicting intensive care relatives at risk of post traumatic stress disorder

C. Jones[1], P. Skirrow[1], R. D Griffiths[1], G Humphris[2], S Dawson[3] and J Eddleston[3]

[1]*Intensive Care Unit, Whiston Hospital, Prescot L35 5DR and Department of Medicine, University of Liverpool, L69 3GA, UK.* [2]*Department of Clinical Psychology, University of Liverpool, L69 3BX, UK.* [3]*Intensive Care Unit, Manchester Royal Infirmary, Manchester M13 9WL, UK*

The aim of this study was to look at the proportion of relatives still anxious at 2 and 6 months post ICU discharge and the incidence of post traumatic stress disorder (PTSD).

Table 12 Association between antidepressant use and length of hospital stay. Mann–Whitney U * $Z = -2.289$, $P = 0.021$, ** $Z = -3.156$, $P = 0.002$, *** $Z = -2.616$, $P = 0.009$

Patient characteristics	Antidepressants (n = 18)	No antidepressants (n = 58)
ICU stay in days (median, range)	18.5 (5–77)*	8 (1–110)*
Hospital stay in days (median, range)	57.5 (23–217)**	27 (12–257)**
Depressed 2 weeks post ICU (HAD >10)	5 (28%)	8 (14%)
Premorbid panic attacks/phobias	3	5
Premorbid depression	1	3
Post hospital discharge		
Fear questionnaire at 2 months	32 (0–64)***	10 (0–61)***
Depressed at 2 months (HAD >10)	4 (22%)	7 (12%)
SF-36 physical role at 2 months (median, range)	25 (0–90)	30 (0–100)

Table 13 Level of anxiety among relatives

Psychological variable	2 months ($n = 54$)	6 months ($n = 38$)
Very anxious (HAD >10)	15 (28%)	12 (32%)
IES scores (median, range)	29.5 (0–62)	33.5 (0–69)
Possible PTSD IES scores >21	32 (60%)	20 (37%)

Anxiety amongst relatives of intensive care (ICU) patients is understandable while patients' remain critically ill and 60% of relatives remain anxious at 2 weeks post ICU discharge.[1] However the longer term psychological consequences of this degree of prolonged stress have not been examined.

The closest relative of recovering ICU patients was approached once it was clear the patient was recovering and expected to survive to 6 months. Anxiety was assessed using the Hospital Anxiety and Depression Scale (HAD) and vulnerability to PTSD using the Impact of Event Scale (IES).

Fifty-four ICU patients and their closest relative were interviewed at 2 months, but only 38 relatives completed questionnaires at 6 months All the patients had been intubated and had had an ICU stay ≥48 h with a median APACHE II score 16. While the level of anxiety amongst relatives was reduced from that seen at 2 weeks a third still remained very anxious at 2 and 6 months (see Table 13).

IES scores at 6 months were predicted by the IES scores at 2 months and anxiety at 2 weeks and at 2 months (ANOVA P = 0.0001, 0.007, 0.05 respectively).

Of the 20 relatives with high IES scores at 6 months, all reported intrusive memories of ICU and avoided reminders of the experience. All these relatives had been very anxious at 2 weeks post ICU; however 60% of relatives were anxious at this point. To increase the predictive power relatives with HAD anxiety scores of >13 at 2 weeks were examined; of these 12 had high IES scores at 6 months and three did not.

This study suggests that anxiety levels amongst close relatives of ICU patients remains high for several months after discharge from ICU. The predictive power of early anxiety, particularly HAD scores >13, and the IES at 2 months for later psychological morbidity could allow the targeting of an intervention, such as counselling, with the aim of preventing the development of established PTSD in relatives of ICU patients.

Keywords: intensive care, audit; complications, post traumatic stress disorder

Reference

1 Jones C, Griffiths RD, Humphris GH. *Br J Anaesth* 1999; **82**: 797P

Combined high frequency ventilation and kinetic therapy for the management of severe hypoxia in adult respiratory distress syndrome

P. Gayatri and D. Higgins

Anaesthetic Department, Southend Hospital, Prittlewell Chase, Westcliff on Sea, Essex SS0 0RY, UK

Pressure controlled inverse ratio ventilation (PCIRV) is often used as the initial therapeutic manoeuvre to improve oxygenation in severe adult respiratory distress syndrome (ARDS). When this alone fails, however, there is no consensus as to which therapy to resort to. We have used combined high frequency ventilation (CHFV) along with kinetic therapy (KT) to treat three patients with ARDS and resistant hypoxia. The basis for this treatment was our previous clinical observation that the two techniques together produced a greater improvement in oxygenation than either used alone.

Table 14 Effect of therapy on oxygenation in the three patients

	Stage of therapy	Pa_{O_2}/FI_{O_2}
Patient 1	(a) PCIRV alone	7.3
	(b) 1 h	24.4
	(c) 24 h	31.06
Patient 2	(a) PCIRV alone	12.2
	(b) 1 h	18.5
	(c) 24 h	23.5
Patient 3	(a) PCIRV alone	12.7
	(b) 1 h	17.2
	(c) 24 h	20.0

In CHFV a Monsoon jet ventilator was used to superimpose high frequency jet ventilation (rate 300 cycles min^{-1}, inspiratory time 0.3, driving pressure 1 bar) on pressure controlled ventilation (rate 10 breaths min^{-1}, inspiratory pressure 30 mbar). At the same time patients were positioned on a kinetic therapy pressure relief low air-loss bed (KCI) and rotated through a total angle of 90°. Three Pa_{O_2}/FI_{O_2} values for each patient are shown in Table 14 and these correspond to (a) PCIRV alone (b) after 1 h of combined therapy and (c) after 24 h of combined therapy.

The combination of CHFV with kinetic therapy produced improvement in oxygenation in all patients. Each of these individual therapies is believed to act through a different physiological mechanism.[1 2] It is possible that the two together may, therefore, produce greater improvement than either therapy applied on its own. The number of such cases that present to one institution limits our small study, but we believe the significant improvement in oxygenation warrants further investigation.

Keywords: complications, adult respiratory distress syndrome

References

1 Lanzenberger-Schragl E, Donner A, Kashanipour A, *et al. Acta Anaesthesiol Scand* 1996; **109**: 157–60

2 Bein T, Reber A, Metz C, *et al. Intensive Care Med* 1998, **24**: 132–7

P300 evoked by the patient's name as a predictor of recovery from coma

T. P. Simpson[1], N. M. Kane[2], R. L Barton[3], C. A Rowlands[3], A. R. Manara and S. R. Butler[3]

[1]Intensive Care Unit, [2]Department of Neurophysiology, Frenchay Hospital, Frenchay Park Road, Bristol BS16 1LE, UK [3]Burden Neurological Institute, Stoke Lane, Bristol BS16 1QT, UK

An assessment of event related potentials in response to a series of clicks or tone bursts has been shown to be a highly specific predictor of recovery from coma caused by head injury.[1] There is anecdotal evidence that patients in coma may be roused by emotionally significant stimuli like the sound of their own name. In non-attending normal subjects, the electrical response to the sound of their own name among a series of abstract tones includes both the 'mismatch negativity' (a protracted negativity following the N1 component of the auditory evoked response) and subsequently a P300. The latter is generated by mechanisms involved in recognizing the meaning of a stimulus. We hypothesized that such stimuli may be more powerful probes of residual function and thus more sensitive predictors of recovery from coma than responses to simple tones.

We recorded the responses to tone bursts interspersed at irregular intervals with the person's name (spoken by a relative) in 21

Table 15 The incidence of P300 evoked by the patient's name in those who survived and those who died

	Recording early in coma		Best recording during coma	
Outcome	**P300 absent**	**P300 present**	**P300 absent**	**P300 present**
Alive	6	6	2	10
Dead	9	0	9	0

patients in coma (Glasgow Coma Score (GCS) ≤8 post-resuscitation) due to head injury (14), subarachnoid haemorrhage (6) and hepatic encephalopathy (1).

Mean GCS on admission of the 21 patients was 4.4 (SD2.0). The initial recording was made within 3–4 days of onset, and subsequent recordings were made twice weekly until recovery of consciousness or treatment was withdrawn. Outcome was assessed at 6 months on the Glasgow Outcome Score (GOS). Of the 12 patients who survived, five had a GOS of 5 (Good Recovery), five a score of 4 (Moderate Disability) and two had a score of 3 (Severe Disability).

Table 15 shows the incidence of P300 evoked by the patient's name in those who survived and those who died. Eventually it was present in all but two who made a good recovery and none of those who died All of those in whom P300 was present survived; however its absence early in coma is not predictive.

Keywords: complications, coma; recovery; nerve, potential

Reference

1 Kane NM, Curry SH, Manara AM *et al* *Intensive Care Med* 1996; **22:** 39–46

The protective effect of cuff lubrication in critically ill patients with tracheostomies

P. J. Young, K. Burchett and M. C. Blunt

Intensive Care Unit, Queen Elizabeth Hospital, Gayton Road, King's Lynn PE30 4ET, UK

Aspiration of infected secretions past the tracheal tube cuff causes ventilator associated pneumonia (VAP).[1] This aspiration occurs despite an adequate intracuff pressure, because the fluid leaks along longitudinal folds within the wall of a high volume low pressure (HVLP) cuff.[2] Previous *in vitro* work has suggested that KY jelly cuff lubrication might prevent this leakage by physically blocking the folds.[3] The objective of this study is to quantify the effect of cuff lubrication on subglottic to tracheal dye aspiration in critically ill patients with tracheostomies.

Methods: This is a prospective open observational study Seventeen critically ill patients who required a tracheostomy were recruited. All the study patients initially received a size 8 mm ID Portex Profile cuffed tracheostomy tube at percutaneous tracheostomy by the Grigg's technique. Lubrication was determined by the preference of the clinician performing the percutaneous tracheostomy. All the tracheostomy tubes had been modified by the addition of a fine bore catheter that was glued above the cuff to enable dye instillation into the subglottic space. The cuff was inflated to 30 cm H_2O (2.9 kPa) and maintained at this pressure by intermittent checks prior to dye instillation and 8 hourly using a cuff inflator (Portex, UK). Blue food dye (E122) 0.5 ml followed by saline 3 ml was instilled daily through the catheter into the subglottic space. The nurse responsible for the patient was instructed to report dye obtained from tracheal aspirates (performed post instillation and at least 4 hourly thereafter). Tracheobronchial aspiration was deemed to have occurred if dye was retrieved from the trachea. The Wilcoxon rank sum test was used for the data analysis

Results: Sixteen of the 17 cuffs leaked after a median of 1 day. One cuff did not leak despite 10 days of testing. Of the cuffs that leaked, nine cuffs were lubricated and leaked after a median of 2 days (range 1–5) and seven cuffs were not lubricated and leaked after a median of 1 day (0–1). Lubrication thus appeared to protect against leakage for longer than non-lubrication ($P<0.05$, Wilcoxon rank sum test for unpaired samples).

Conclusion: This study suggests that cuff lubrication affords protection against aspiration for 1–5 days. Clinicians should be aware that a HVLP cuff cannot reliably prevent the transit of fluid from the upper airway to the lungs after a median of 2 days even with lubrication. Occasionally a HVLP cuff will be an exact fit for the trachea in which it is inflated and folds will not form in the cuff wall. In this circumstance leakage is prevented. It is likely that the one cuff that did not leak despite 10 days of testing was an exact fit for that patient's trachea. Until a cuff is available that prevents aspiration at acceptable tracheal wall pressures we would recommend that all tracheal and tracheostomy cuffs are lubricated with KY jelly prior to insertion

Keywords: cuffs, tracheal, intubation tracheal, complications; complications, intubation tracheal

Acknowledgement

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References

1 Craven DE. *Ann Intern Med* 1995; **122:** 229–31
2 Seegobin RD, Van Hasselt GL *Can Anaesth Soc J* 1986; **33:** 273–9
3 Young PJ, Rollinson M, Downward G, Henderson S *Br J Anaesth* 1997, **78:** 557–62

Ultrasonography of the femoral vessels in the groin: implications for vascular access

P. Hughes, C. Scott and A Bodenham

General Intensive Care Unit, The General Infirmary at Leeds, Great George Street, Leeds LS1 3EX, UK

The femoral artery and vein are commonly used to access the circulation.[1] Accidental puncture of one vessel whilst attempting to cannulate the other occurs commonly. Ultrasound is a useful tool to assist cannulation of vessels.[2] Clinical use of ultrasound by us casts doubt on the accepted belief that anatomically the two vessels lie side by side. Using ultrasound we imaged these two vessels in the groin, to determine the optimal site for percutaneous cannulation that would reduce the risk of hitting the other vessel.

Approval for the study was obtained from the local ethics committee. Fifty consecutive admissions to general or neurosurgical intensive care were studied. Patients were excluded if they already had femoral vascular cannulae, a history of pelvic trauma, or recent vascular surgery involving the femoral vessels. Patients were examined supine by one of the authors using a portable ultrasound machine and a 7.5 MHz linear probe (Scanner 100, Pie Medical Ltd, Crawley, UK). Both groins were examined in each patient. The position of the inguinal ligament was defined by taking a straight line from pubic tubercle to anterior superior iliac spine. The vessels were located in cross section and ultrasound images were obtained at the level of the inguinal ligament then 2 cm and 4 cm below it. The size, separation and depth of the vessels together with the extent to which one vessel overlapped the other were measured. The position of surface anatomical landmarks and the level of the division of the common femoral artery as seen on ultrasound were recorded. Analysis of the data describing the anatomical relationships observed was performed using a Chi-squared test.

The vessels were easily visualized in all but one patient. In most patients there was some degree of overlap of the artery over the vein. This frequency and degree of overlap increased as the vessels descended into the thigh. At the level of the inguinal ligament in the majority of patients there was no vessel overlap observed (in 72% of the patients on the right side and 59% on the left side). In virtually all the patients 4 cm below the ligament some degree of overlap was observed (100% of patients on the right side and 96% on the left side), and in approximately half of the patients the overlap was complete (50% and 45% on the right and left respectively). Chi-squared analysis of the data-table describing the pattern of overlap related to distance below the inguinal ligament showed that the relationship observed was statistically significant on both sides ($P<0.05$).

To avoid damage to the neighbouring vessel percutaneous access should be undertaken just below the inguinal ligament as defined by a straight line from pubic tubercle to anterior superior iliac spine. The anatomical variation and difficulty in establishing external landmarks suggests that ultrasonography should be used more frequently to aid accurate placement, particularly in the higher risk patient with difficult anatomy, coagulopathy or peripheral vascular disease

Keywords: arteries, cannulation; equipment; measurement techniques, ultrasound; veins, cannulation

References

1 Smyrnios NA, Irwin RS. *Crit Care Med* 1997; **25**: 1943–6
2 Kwon TH, Kim YL, Cho DK. *Nephrol Dial Transplant* 1997; **12**· 1009–12

Undergraduate education on the intensive care unit

M Ashton and **M. P. Shelly**

Intensive Care Unit, Withington Hospital, Nell Lane, Manchester M20 2LR, UK

The Intercollegiate Board for Training in Intensive Care Medicine has recommended that medical students should be exposed to a period of structured training in intensive care.[1] The importance of training in the management of the critically ill patient has also been emphasized by the General Medical Council.[2] The current state of medical student training in intensive care is not known. We performed a questionnaire study to investigate the level of undergraduate experience of intensive care nationally.

A questionnaire was sent to the director of each intensive care unit (ICU).[3] The questionnaire asked about the number of medical students attached to the ICU, the duration of the attachments, teaching and assessment procedures and satisfaction with the present situation. It also asked about potential problems experienced by medical students. Another questionnaire was piloted to groups of first and fourth year medical students. This questionnaire asked about the usefulness of undergraduate intensive care training, the students experience of such training and possible problems.

The response rate for the ICU questionnaire was 155/267 (58%). Medical students were attached to 79 (51%) of responding ICUs, 26 (33%) of attachments were for one day and 73 (92%) for a month or less. Of the units offering attachments, 50 (63%) receive 10 students or fewer each year and 15 (19%) receive more than 25 students annually. One unit offered a first year attachment; 53 (68%) offered final year attachments. During the attachments, 57 (72%) of units gave up to 5 h of teaching each week and 42 (43%) assessed the students during the module, usually by a written report. Of the respondents 39 (49%) were dissatisfied with the level of intensive care experience gained by students and most thought intensive care was a vital part of undergraduate training. The technical atmosphere and clinical complexity of intensive care were thought to be potential problems by 40% and 36% of respondents. Twenty-five first year and 25 fourth year medical students completed the student questionnaire. Of these, 46 (92%) thought it should be possible to spend some time on the ICU before graduating and 47 (94%) thought the third year the most appropriate time. More students (41 (82%)) believed that the technology and complexity of intensive care were important problems in intensive care teaching.

Few medical students are exposed to intensive care during their undergraduate training and then for only a short time. There is dissatisfaction from students and intensivists with the current level of undergraduate intensive care experience. The technology of intensive care and the complexity of the clinical problems are perceived as problems by students but not by clinicians. The ICU is a valuable resource for training knowledgeable, skilful doctors; at present that resource is underused.

Keywords: education, medical students; intensive care

References

1 *Recommendations* Intercollegiate Committee for Training in Intensive Care Medicine
2 *The New Doctor.* General Medical Council
3 *Directory of Emergency and Special Care Units 1999.* CMA Medical Data, Cambridge

The perceived and actual use of healthcare resources following intensive care

K. E. Hawes, C. Kneebone and **M. P. Shelly**

Intensive Care Unit, Withington Hospital, Nell Lane, Manchester M20 2LR, UK

Intensive care is often viewed as expensive and cost benefit analysis has become an essential part of its evaluation. Initially simple mortality statistics were used but now more complex measures such as quality of life[1] scores are employed. The complex physical and psychological consequences of an episode of critical illness may influence the patient's quality of life.[2] Their use of healthcare resources may reflect their health needs and this has the potential for considerable resource and cost implications.[3] This pilot study was performed to investigate the perceived and actual use of healthcare resources by patients following an episode of critical illness.

Surviving patients were identified who had spent more than 4 days on the intensive care unit (ICU) and been discharged 6–12 months earlier. The patients were interviewed using a semi-structured format. Questions were asked about their use of healthcare resources since discharge compared with a period before their ICU admission. A perceived quality of life scale was completed and details of the patient's employment status were recorded. At the interview, consent was obtained from the patient to refer to their medical records and note their actual healthcare use.

Seventeen patients (10 men) were interviewed, aged 59 (31–77) (median (range)). There was a significant increase in both the perceived and actual use of healthcare resources since discharge from the ICU. This increase was in both the number of different healthcare workers seen (1.82 *vs* 5.18 mean number of healthcare workers/patient; 65% increase; $P<0.0001$) and the number of visits made (1.88 *vs* 4.88 mean number of outpatient appointments/patient; 61% increase; $P = 0.004$). The patient's perceived quality of life had decreased significantly following their critical illness

(82.3 *vs* 66.1%; 16.2% decrease; $P = 0.005$). Employment status also changed with a significant increase in those retired or disabled. The use of healthcare resources correlated with the age of the patient ($P = 0.022$) and their change in perceived quality of life (0.04).

This pilot study demonstrates that health is an important issue for patients following intensive care. In the 6 months after discharge from the ICU, the majority of patients continue to experience health problems. This is reflected in their increased use of healthcare resources and their reduced quality of life. The provision of healthcare for this group has significant resource and cost implications.

Keyword: intensive care

References

1 Brooks R, Bauman A, Daffurn K, Hillman K. *Clin Intensive Care* 1995; **6**: 127–35

2 Capuzzo M, Bianconi M, Contu P, et al *Intensive Care Med* 1996; **22**: 947–53

3 Jacobs CJ, Van der Vilet JA, Van der Roosendaal MT, et al. *Intensive Care Med* 1988; **14**. 217–20

Post mortem findings reveal major diagnostic errors in one fifth of patients who die in a critical care unit

S. Twigg, A. McCrirrick and **P. Sanderson**

Intensive Care Unit, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL1 3NN, UK

A study was performed to determine the accuracy of clinical diagnosis compared with post mortem findings in a nine bed combined high dependency and intensive care unit in a district general hospital (DGH). One hundred and two consecutive post mortem examinations, performed over a 3-yr period, were analysed using a retrospective and blinded review of medical records. All notes relating to post mortem findings were removed from the medical records which were then reviewed by an intensive care consultant. Cause of death and major clinical diagnoses were determined and compared with post-mortem findings.

All patients in whom a discrepancy was found had their cases reviewed by a panel of three intensive care clinicians and a consultant surgeon to determine the significance of the discrepancy using the Goldman classification.[1] A Goldman I discrepancy is a missed major diagnosis that if known in life would have altered therapy and possibly survival. A Goldman II discrepancy is a missed major diagnosis that would not have altered therapy or survival.

Between June 1996 and May 1999 there were 1718 admissions and 252 deaths (14.7%), of which there were 102 post mortems performed (post mortem rate of 40.5%). Two patients were excluded, being under 16 yr of age, and the notes of three patients were unobtainable

Of the 97 patients, 4 (4.1%) had Goldman I discrepancies, and 19 (19.6%) had Goldman II discrepancies. Complete agreement between pre and post mortem diagnosis was found in 74 (76.3%). Discrepancies fell into four main groups, unrecognized haemorrhage (7 patients), pulmonary emboli (5), myocardial infarction (5), and infectious complications (4). There was a higher proportion of surgical patients with discrepancies (discrepancies in 13 out of 30 surgical patients, 43%), compared with medical patients (7 out of 40, 18%). The four Goldman I discrepancies were unrecognized gastrointestinal haemorrhage, untreated pulmonary embolus, missed septic arthropathy and unrecognized valvular heart disease

This is the first analysis of discrepancies in post mortem findings in a DGH critical care unit (CCU). Previous studies have concentrated on specialized tertiary referral centres.[2–4] There are a higher number of unrecognized haemorrhagic complications than in previous studies.[2–5]

This study reveals that in a CCU important diagnostic errors were made in 19.6% of all patients who subsequently die. In a fifth of these (4.1%), diagnostic errors may have adversely affected their survival Post mortem examinations have a significant part to play in auditing clinical practice and diagnostic performance in intensive care medicine.

Keywords: intensive care; audit

References

1 Goldman L, Sayson R, Robbins S, et al. *N Engl J Med* 1983; **308**: 1000–5

2 Mort T, Yeston N. *Crit Care Med* 1999; **27**: 299–303

3 Goldstein, Brahm, Metlay, et al *Crit Care Med* 1996; **24**: 683–6

4 Blosser, Sandralee A, Zimmerman et al *Crit Care Med* 1998; **26**: 1332–6

5 Barendregt WB, de Boer HHM, Kubat K. *Br J Surg* 1992; **27**: 1297–9

Response to inhaled nitric oxide in patients with ARDS and renal failure

C. N. H. Tan, J. Scott and R. Wenstone

Intensive Care Unit (ICU), the Royal Liverpool University Hospital (RLUH), Prescot Street, Liverpool L7 8XP, UK

Inhaled nitric oxide (NO) has successfully been shown to improve oxygenation in patients with acute respiratory distress syndrome (ARDS).[1] This success has not been matched by reduced mortality.[2] In many of these studies, poor outcome has been influenced by the poor prognosis of underlying conditions e.g. multiple organ dysfunction syndrome.[3] We aim to show that patients in renal failure are much less likely to respond to NO compared to those with normal renal function, and that our use of NO in patients with renal failure was associated with high mortality.

Method: Between January 1996 and January 1999, data were collected on patients treated for ARDS with inhaled NO on the ICU at the RLUH. Patients were treated according to the UK guidelines for the administration of NO in adult ICUs.[4] Patients were included if they had a Pa_{O_2}/FI_{O_2} ratio of <200 (mmHg) with X-ray evidence of ARDS including bilateral pulmonary infiltrates. Renal failure was defined by decreased urine output (<400 ml day^{-1}) along with raised serum creatinine of ≥200 µmol litre^{-1}. No distinction was made between acute or chronic renal failure. An in-house purpose built continuous-flow system was used to deliver NO into the inspiratory limb of the ventilator circuit, distal to the humidifier. NO and nitrogen dioxide were monitored using chemo-luminescent sensors 'Micromedical Printernox' placed at the Y-piece of the circuit. The flow of NO was adjusted to maintain a measured value of 10–20 ppm. A patient was regarded as having responded to NO if the Pa_{O_2}/FI_{O_2} ratio improved by ≥20% in the first 24 h of therapy.[4] A patient was regarded as a survivor if they were discharged alive from ICU.

Results: 28 patients received inhaled NO. Twelve (42%) of these

Table 16 Mortality figures

No. of deaths/total no. of patients in the group	Responders ($n = 21$)	Non-responders ($n = 7$)
Without renal failure	6/14 (42%)	2/2 (100%)
With renal failure	4/7 (57%)	5/5 (100%)

patients had renal failure. Of the 16 patients without renal impairment, 14 (88%) responded to NO. Only 7/12 (58%) responded in the renal failure group. Mortality figures are shown in Table 16.

All non-responders to NO with renal failure died. All patients ($n = 5$) who initially responded to NO and had normal renal function, but whom later developed renal failure also died.

Conclusion: In our study, patients with ARDS and renal impairment were less likely to respond to inhaled NO than those with ARDS and normal renal function (58 *vs* 88%; $P<0.05$). Patients with renal failure who did not respond to inhaled nitric oxide had 100% mortality.

Keywords: complications, acute respiratory distress syndrome; complications, renal; pharmacology, nitric oxide

References

1 Troncy E, Collet JP, Shapiro S *et al.* *Am J Respir Crit Care Med* 1998; **157**: 1483–8
2 Dellinger RP, Zimmerman JL *et al.* *Crit Care Med* 1998; **26**: 1–2
3 Suchyta MR, Grissom CK *et al.* *Intensive Care Med* 1999; **25**: 538–9
4 Cuthbertson BH, Dellinger P *et al.* *Intensive Care Med* 1997, **23**: 1212–18

Respiratory failure and intraoperative oxygenation following oesophagectomy

S. P. Tandon, R Bullock, A. Batchelor, A Gascoigne, I. Warnell, I. Shaw, N. Hayes, S M. Griffin and S. V. Baudouin

Department of Anaesthesia and Intensive Care and Northern Oesophago-Gastric Cancer Unit, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, UK

Respiratory complications are a major cause of morbidity and mortality following oesophagectomy.[1] We hypothesized that patients who develop postoperative respiratory failure would have an unstable intraoperative course. Two stage oesophagectomy requires a period of one lung ventilation (OLV) and one measure of intraoperative instability is desaturation during OLV. We therefore studied the relationship between Sa_{O_2} during OLV and postoperative course. Previous work has focused on preoperative factors associated with postoperative complications.[2] There is little information on intraoperative factors that may influence outcome.

We performed a retrospective analysis of all elective oesophagectomies performed between January 1998 and August 1999. Seventy-seven patients had a 2-stage sub-total oesophagectomy requiring OLV. Oxygen saturation recorded on the anaesthetic chart during OLV was plotted on a fixed linear scale of 0–100% against time for each patient. The area above the curve was calculated, as a measure of intraoperative oxygenation during OLV. This was standardized by dividing the area by the OLV duration, thus obtaining the Area Per Unit Time (APUT). The postoperative course of each patient was recorded including outcome, total duration of ITU stay and the worst Pa_{O_2}/FI_{O_2} ratio attained. ARDS was defined using the American-European Consensus Conference on ARDS criteria. Twenty-one patients had a prolonged ITU stay (>48 h) and all had a persistent Pa_{O_2}/FI_{O_2} <27 Thirteen patients (17% of the total) fulfilled the Consensus Conference criteria for ARDS and seven of these died in hospital.

Table 17 APUT and OLV time data for patients with and without ARDS

	Patients without ARDS (n = 64)	Patients with ARDS (n = 13)	*P* value
Mean APUT (SE)	3.4 (0.3)	5.5 (0.9)	0.004
Mean OLV time (SE)	130 (4) min	141 (7) min	0.17

Total OLV time was not significantly different between the groups but patients who developed ARDS had significantly greater intraoperative hypoxaemia as measured by the APUT (Table 17) We conclude that intraoperative hypoxaemia is associated with respiratory failure following oesophagectomy.

Keywords: complications, adult respiratory distress syndrome; gastrointestinal tract, oesophagus

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References

1 Dumont P, Wihlm JM, Hentz JG, Roeslin N, Lion R, Morand G. *Eur J Cardio-thorac Surg* 1995, **9**: 539–43
2 Kuwano H, Sumiyoshi K, Sonada K. *Eur J Surgery* 1998; **164**: 581–6

Tracheal rupture during percutaneous tracheostomy. Safety aspects of the Griggs method

M. P. R. Watters, G. Thorne, C M. Cox and C. R Monk

Department of Anaesthesia, Bristol Royal Infirmary, Bristol BS2 8HW, UK

Despite being used in many intensive care units in the UK,[1] little is known about the safety of the guide wire dilating forceps (GWDF) technique of percutaneous tracheostomy. A previous evaluation study of the GWDF noted a definite learning curve in knowing how much force to exert through the forceps to establish a therapeutic dilation.[2] The aim of this study was to determine how similar the force required for therapeutic dilation of the trachea is to the force required to cause tracheal disruption using the GWDF.

Percutaneous dilational tracheostomy using the GWDF was performed on 12 cadavers scheduled to undergo post mortem the same day. Dilational forces and distances were measured as electric signals (mV) using specially monitored forceps, the change in mV being proportional to the change in both distance and force Three related force and distance measurements were recorded.

(1) Dilation of the pretracheal tissues.
(2) Therapeutic dilation of the trachea. The trachea was dilated to allow easy insertion of a 7-mm internal diameter low profile cuffed tracheostomy tube (Mallinckrodt, UK).
(3) Destructive dilation of the trachea. The trachea was dilated until there was a distinct give and the investigator felt that disruption had occurred to the trachea.

Forces were compared using Student's *t*-test.

The force required for tracheal destruction was more than twice that required for therapeutic dilation 735 ± 140 *vs* 296 ± 80 mV ($P<0.001$) (Figure 1). Therapeutic tracheal dilation requires less force than is required for dilation of the pretracheal tissues 296 ± 80 *vs* 417 ± 160 mV ($P<0.05$).

The marked differences seen between the forces required for therapeutic and destructive dilation of the trachea offer a reasonable margin of safety when using the GWDF. Dilating the pretracheal tissues is a useful guide as less force should then be used to dilate the trachea.

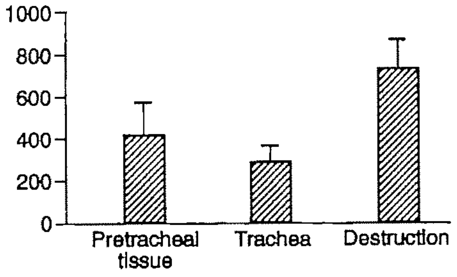

Fig 1 Force required (mV) to dilate the pretracheal tissue and the trachea, and to cause tracheal destruction.

Keywords: equipment, tracheostomy

References

1 Cooper RM. *Anaesthesia* 1998; **53**: 1209–12
2 Caldicott LD, Oldroyd GJ, Bodenham. *Anaesthesia* 1995; **50**: 49–51

Acidaemia is less severe following reperfusion via the hepatic artery compared with the portal vein during liver transplantation

T. S. Walsh[1], O. J. Garden[2] and A. Lee[1]

Department of [1]Anaesthetics and [2]Surgery and the Scottish Liver Transplant Unit, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW, UK

Reperfusion of the liver during transplantation can cause cardiovascular changes such as systemic vasodilatation, pulmonary hypertension and cardiac dysfunction. We have previously demonstrated a slower increase in oxygen consumption when the hepatic artery was used for reperfusion rather than the portal vein, and had the clinical impression that overall patient stability was greater with the former technique.[1] We therefore compared the acid–base changes which occur following reperfusion with each of these techniques.

Twenty patients undergoing liver transplantation were studied. In all cases the piggyback technique was used, and anaesthetic management was similar. In 10 patients liver reperfusion was first via the portal vein followed by the hepatic artery; in the other 10 patients the hepatic artery was anastomosed first followed by the portal vein. Ventilation remained constant during the study period. Arterial blood was drawn for acid–base and whole blood lactate measurement at three time points: (1) immediately prior to reperfusion, (2) 30 min after reperfusion, (3) 60 min after reperfusion. Changes in variables were compared between the groups by Mann–Whitney U test corrected for multiple tests using the Bonferroni method.

Data are shown in Table 18. All acid–base variables were similar between the groups prior to reperfusion. Following reperfusion acidaemia (H^+ concentration) was more marked in the portal vein group and was accompanied by a larger increase in Pa_{CO_2}. Changes in blood lactate and acidosis (Standard Bicarbonate Concentration) were similar between the groups.

Our data indicate that a smaller acid load is released into the systemic circulation immediately after reperfusion when the hepatic artery is anastomosed first rather than the portal vein, as is conventional. This may be because the release of ischaemic metabolites from the splanchnic circulation is delayed, or because the rate of flushing of acid from the donor liver is slower via the hepatic artery which has a lower overall flow and is a higher resistance circulation. Less marked acidosis and hypercapnia are potentially beneficial particularly in high risk patients, such as those with fulminant hepatic failure who are at risk of intracranial hypertension following reperfusion.

Keywords: liver, oxygen consumption, surgery, transplantation

Reference

1 Walsh TS, Forrest G, Hopton P *et al. Intensive Care Med* 1997; **23** (suppl 1): S95

Table 18 Acid–base variables for patients undergoing liver reperfusion via the hepatic artery (HA, $n = 10$) or portal vein (PV, $n = 10$) during liver transplantation All values median (1st, 3rd quartile) $^*P<0.02$ between HA and PV groups

	Baseline values		**Change time point 1–2**		**Change time point 2–3**		**Timepoint 3 values**	
	HA	**PV**	**HA**	**PV**	**HA**	**PV**	**HA**	**PV**
Lactate	1.55	1.90	0.93	0.77	−0.16	−0.24	2.54	2.20
mmol litre^{-1}	[0.88,3.81]	[1.75,2.09]	[0.29,1.23]	[0.59,1.21]	[−0.54,0.71]	[−0.41,−0.12]	[2.14,3.01]	[1.87,3.34]
SBC	22.3	22.1	−1.65	−1.10	0.30	1.15	20.7	22.2
mmol litre^{-1}	[20.5,23.3]	[21.0,23.6]	[−2.18,−0.83]	[−2.00,−0.90]	[−1.2,0.88]	[0.73,1.4]	[18.8,21.9]	[20.8,24.1]
H^+	40.0	42.1	4.45	10.75	3.00	−5.1*	51.3	49.5
nmol litre^{-1}	[37.1,44.5]	[40.9,47.0]	[3.03,8.58]	[7.28,14.03]	[−0.95,9.68]	[−8.60,−2.75]	[44.5,54.7]	[43.0,52.8]
Pa_{CO_2}	4.12	4.67	0.29	1.01*	0.56	−0.02*	5.27	5.57
k*Pa*	[3.88,4.56]	[4.34,4.96]	[0.18,0.59]	[0.74,1.55]	[0.25,0.92]	[−0.29,0.13]	[4.95,5.48]	[5.17,5.79]

Hand grip dynamometry does not correlate with anthropometric measures of nutritional status in survivors of prolonged critical illness

L. Douglas[1], K. C. H. Fearon[2] and T. S. Walsh[1]

[1]Intensive Care Unit and [2]University Department of Surgery, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK

Prolonged critical illness results in malnutrition and functional impairment. Impaired muscle function has several possible explanations in these patients such as reduced muscle mass, myopathy and neuropathy. There are no data regarding the relation between anthropometric measures and measures of muscle strength following critical illness. In other populations mid arm muscle circumference (MAMC, a measure of lean body mass) and muscle strength measured by hand grip dynamometry (HGD, a simple measure of muscle function) correlate. We have investigated the relation between anthropometric measures of nutritional status and muscle strength using HGD in patients attending our Intensive Care follow up clinic.

Thirty patients who spent more than 4 days in Intensive Care (median stay 9.25 days (range 4.4–58.9)) were studied 3 months following ICU discharge. Height, weight, body mass index (BMI), triceps skinfold thickness (TSF), mid arm circumference (MAC) and MAMC were measured using standard anthropometric techniques. Pre-illness weight and BMI were determined

Table 19 Transfusion thresholds Values are median (25–75% quartiles) Inten· intensivists, Haem· haematologists

Trigger	Scenario 1		Scenario 2		Scenario 3		Scenario 4	
	Inten	Haem	Inten	Haem	Inten	Haem	Inten	Haem
Hb g dl^{-1}	9 (8–9 25)	9 (8–10)	10 (9–10)	10 (9–10)	9 (8–10)	10 (9–10)	10 (9–10)	10 (9 125–10)
Platelet count ×10^9 litre^{-1}	51–100	30–50	30–50	30–50				
PT ×control	<2>1.6	<2>1 6						

retrospectively from patient records or recollection. HGD was measured with a single spring hand grip dynamometer. Quality of life was assessed using the SF-36 questionnaire.

A total of 64% of patients had failed to regain the weight recorded prior to admission to ICU; 39% had a persistent weight loss of >10% (mean pre-illness BMI 24.3 (SEM 0.60), 3 month BMI 23.3 (0.51), $P<0.05$). 35% of patients had a TSF <5th centile for the normal population and 25% had a MAMC <5th centile of the normal population. HGD data showed 41% of patients had values <85% of expected values (indicative of significant protein malnutrition in other populations[1]). However, no correlation was found between MAMC and HGD ($r = 0.284$, $P = 0.2$). SF-36 showed 58% of patients perceived their general health to be poor, 57% scored poorly on vitality and 52% on physical function.

Our findings demonstrate marked loss of muscle mass and functional ability using established methods in about one third of patients 3 months following prolonged critical illness. However, unlike other populations MAMC did not correlate with HGD. This may be because (1) factors other than muscle mass contribute to functional impairment following critical illness such as neuropathy and myopathy (2) HGD is too insensitive or effort-dependent in this population. Evaluation of neuromuscular physiology should be included in studies of functional recovery from critical illness More rigorous measures of functional ability are needed in order to understand and improve recovery from prolonged critical illness.

Keywords: intensive care, audit; measurement techniques

Acknowledgement

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Reference

1 Gray CE, Gray IK. *JPEN* 1979; **3**: 366–8

Transfusion practices survey in critically ill patients

H Boralessa, **M. P. Rao**, C. Morgan, N. Soni, D. Goldhill, S. Brett, M. Smith, D. Watson, M. Contereras and H. Boralessa

North Thames Blood Interest Group

There are no published guidelines for the use of red cells, platelets and fresh frozen plasma (FFP) in critically ill patients. This study aimed to examine the attitudes of intensivists and haematologists to the use of blood and blood products.

A scenario based postal questionnaire used previously to elicit transfusion practices of Canadian critical care physicians[1] was modified to assess current practice of red cell, platelet and FFP use in intensive care. Four hypothetical scenarios: trauma (1), sepsis (2), pneumonia (3) and acute bleeding (4) were described. Each scenario had a series of clinical situations commonly seen in critically ill patients. The questionnaire was circulated to the directors of intensive care units and haematologists in charge of blood banks in all hospitals in England. Data were analysed using Wilcoxon matched-pairs test, Friedman two-way ANOVA and Mann–Whitney U test.

A total of 162 intensivists and 77 haematologists responded.

Baseline transfusion thresholds for red cells ranged from 6 to 12 g dl^{-1}. There was significant ($P<0.005$) interscenario variations. Increasing age, high APACHE score, surgery, ARDS, septic shock and lactic acidosis significantly ($P<0.005$) modified the threshold.

There were greater variations in the baseline threshold for platelet transfusion. A total of 21.5% selected a threshold of <30×10^9 litre^{-1}. Surgery and invasive procedures significantly ($P<0.005$) altered the threshold.

Baseline threshold Prothrombin time (PT) for transfusion of FFP ranged from 1 to >2.5 times control. Bleeding significantly ($P<0.01$) lowered the threshold.

The majority of respondents (72.3%) selected a baseline Hb threshold of 9–10 g dl^{-1} (Table 19). The thresholds for platelets and FFP were far less consistent.

Keywords: intensive care; transfusion

Reference

1 Hebert PC, Wells G, Martin C, et al. *Crit Care Med* 1998; **26**: 482–7

Post-operative renal replacement therapy after coronary artery bypass surgery (CABG) in the UK, is the outlook still bleak?

S. M. A. Hubble, I. M. Davies, I. G. Ryder, S. P. K. Linter and S. J Howell

Bristol Royal Infirmary, Upper Maudlin Street, Bristol BS2 8HW, UK

Renal failure requiring acute haemofiltration occurs in 1–5% of patients after coronary artery bypass graft surgery (CABG). In-hospital mortality is reported between 28 and 63%.[1] Few long term follow up studies have been published and outcome in patients with pre-operative dialysis dependent renal failure is unknown in the UK.

Objectives of the study were to investigate early and late mortality following CABG surgery both in patients requiring acute haemofiltration and those already on chronic dialysis therapy

Forty-six patients who required acute and chronic renal replacement therapies post CABG between June 1996 and May 1999 were identified using the cardiac surgery data base and regional dialysis centre patient records. A control group of CABG patients without renal complications was also assessed. Thirty-day mortality, mortality at 1 yr and mortality rate ratios were examined. Functional quality of life in survivors was assessed using New York Heart Association (NYHA) and modified Karnofsky scores[2] by telephone interview. Pre- and post-operative values were compared. The median follow up time was 469 days with a range of 1–1156 days. All statistical analyses were performed using STATA 6 0 for Windows 95.

Post CABG surgery, acute renal failure requiring haemofiltration still carries a markedly increased risk of death despite better than previously reported in-hospital mortality (Table 20). Over 75% of survivors however report a functionally good quality of life with

Table 20 Outcome from coronary artery bypass graft surgery in patients requiring postoperative renal support therapy

	Controls (normal renal)	Acute post-operative haemofiltration	Chronic haemodialysis patients
Number of patients	51	37	9
In-hospital mortality	0/51	10/37 (27%)	0/9
Mortality at 1 yr	1/51 (2%)	14/37 (38%)	0/9
Mortality rate per 1000 patient days (95% CI)	0.04 (–0.03–0.11)	0.73 (0.35–1.11)	0.21 (–0.21–0.63)
Mortality rate ratio *vs* control		20.3 (*P*<0.000) significant	5.9 (*P* = 0.14) not significant

improved exercise tolerance and only 1 out of 30 renal failure patients describes himself as housebound.

Chronic renal dialysis patients especially have very favourable outcomes, such that mortality rates are not statistically different from the control group.

Keywords: kidney, failure; surgery, cardiovascular

References

1 Conlon PJ, Stafford-Smith M, White WD *et al. Nephrol Dial Transplant* 1999; **14**: 1158–62

2 Owen CH, Cummings RG, Sell TL *et al. Ann Thorac Surg* 1994; **58**: 1729–33

Does increased lactate discriminate between survivors and non-survivors after abdominal aortic aneurysm surgery?

S. Hubble, S. Howell, J. Cloake and A. J. Padkin

Department of Anaesthesia, Bristol Royal Infirmary, Upper Maudlin Street, Bristol BS2 8HW, UK

Blood lactate levels have been correlated with outcome in sepsis,[1] in shock of various causes[1] and following paediatric cardiac surgery.[2] Lactate was not included in the APACHE II score because of practical difficulties with its determination and consequent infrequent measurement in the early 1980s.[3]

Postoperative care following abdominal aortic or iliac aneurysm (AAA) surgery is the commonest reason for admission to UK intensive care units (ICUs). These patients have a high hospital mortality of 21.4% reported from the ICNARC Case Mix Programme.[4] One hundred and forty-four consecutive patients admitted to ICU post-AAA surgery were studied and four measures of lactate recorded from the first 24 h of admission (see Table 21). Four patients had no values recorded. The Wilcoxon rank sum test was used to test for a significant difference in each measure between survivors and non-survivors. The area under the receiver operator characteristic (ROC) curve was calculated for each measure to test discrimination between survivors and non-survivors, where 1 represents perfect discrimination and 0.5 represents no discrimination. STATA 6.0 for Windows 95 was used for all statistical tests.

Increases in all measures of lactate were significantly associated with hospital mortality (probabilities from <0.0001 to 0.0035) (Table 21). The areas under the ROC curves show that all lactate measures discriminated between survivors and non-survivors. The 24-h lactate value provided both the strongest association and the best discrimination. This may be because it is dependent not only on the magnitude of physiological insult but also on the adequacy of, and the response to postoperative treatment. In view of the positive correlation with mortality in this large group of critically ill patients and the now widespread clinical use of lactate measurements, inclusion of the 24-h lactate value should be considered for future scoring systems.

Table 21 Blood lactate concentrations (median (5th–95th centile)) in patients undergoing aortic aneurysm surgery

	Survivors Median (5th–95th centile)	Non-survivors Median (5th–95th centile)	Probability	Area under ROC curve
Admission lactate	1.9 (0.8–10.8)	3.7 (0.9–9.2)	0.0035	0.66
Highest lactate	2.2 (0.8–11.6)	5.1 (1.1–11.1)	0.0001	0.71
Lowest lactate	1.0 (0.5–2.7)	1.3 (0.6–6.1)	0.0020	0.67
24-h lactate	1.2 (0.6–3.1)	1.7 (0.8–9.0)	<0.0001	0.73

Keywords: complications, mortality; surgery, cardiovascular

References

1 Vincent J-L *Acta Anaesthesiol Scand* 1995. **39** (Suppl 107); 261

2 Siegel LB, Dalton HJ, Hertzog JH, *et al Intensive Care Med* 1996: **22**; 1418–23

3 Knaus WA, Draper EA, Douglas PW, *et al. Crit Care Med* 1985: **13**; 818–29

4 Rowan K. Personal communication

Why use more propofol as 2% formulation?

R. K. Singh, S. Simms and P. G Lawler

Intensive Care Unit, South Cleveland Hospital, Marton Road, Middlesbrough TS3 4BW, UK

Propofol is believed to be the most widely used sedative in the adult intensive care unit (ICU). Its pharmacokinetic profile produces easily controllable sedation.[1] Propofol is prepared in 10% intralipid emulsion (0.1 g ml^{-1} of fat). Critically ill patients may have impaired lipid tolerance and they may also be the recipients of total parenteral nutrition, hence, 'creaming' may be a consequence.[2] Because of the problem of fat load we chose to introduce 2% formulation. We observed that waking of some patients using 2% propofol was delayed and the total cost of propofol supplied increased. The cause for this was not clear.

We retrospectively surveyed our use of propofol during periods of changeover from 1 to 2%. We reviewed the ICU charts of all patients admitted from September 1998 to February 1999 who received propofol (either 1% or 2%) with or without alfentanil. Patients receiving midazolam, fentanyl, morphine or other sedatives were excluded from the study. The sedation scores were noted at 12 noon (period of activity) and 12 midnight (period of quietness) each day. APACHE II diagnosis and APACHE II scores

Table 22 Comparison of 1% with 2% propofol *Garcia-Lawler sedation score is used routinely in this ICU

	1% Propofol	2% Propofol
Number of patients	22	43
Sex (M/F)	13/9	30/13
Age range (median)	24–84 (68)	18–83 (64)
Midday Garcia-Lawler sedation score* range	6–6	2–9
Midnight Garcia-Lawler sedation score range	2–2	1–9
Mean alfentanil consumption (mg h^{-1})	1.25	1.30
Mean propofol consumption (mg h^{-1})	108.95	145.13

were also noted. We calculated propofol and alfentanil consumption for the patients who received 1% or 2% propofol.

Our results demonstrate that patients receiving 1% infusion received 75% of the dose of those receiving 2% propofol (Table 22). The dose of alfentanil used was not significantly different in each group ($P>0.05$). In a 24-h period sedation using 2% propofol cost £18.83 more than when using 1% preparation. This excludes the additional cost of any wasted drug.

This may be because of differences in availability and activity of propofol in a concentrated emulsion, by chemical loss due to deterioration of the drug or by the way drug was administered. The record of sedation scores suggests that the level of sedation fluctuated more when 2% was used. We speculate that alteration to the amount of propofol given is made in increments of 1 ml irrespective of concentration of propofol used. Changing staff practices to alter infusion rates in 10 mg increments may produce less variation in sedation scores.

Keywords: anaesthetics, i.v., propofol; sedation

References

1 Newman LH, McDonald JC, Wallace PGM. *Anaesthesia* 1987; **42**: 929–37
2 Gempeler F, Elston AC, Thompson SP, *et al.* *Anaesthesia* 1994; **49**: 17–20

The predictive value of the base deficit for the cardiac index in post-arrest patients in the intensive care unit

M. Z. Hashemi and **I. W. McConachie**

Department of Anaesthetics, Blackpool Victoria Hospital, Blackpool FY3 8NR, UK

We undertook a retrospective clinical study to determine the relationship of the calculated base deficit and cardiac index in post cardiac arrest patients admitted to the intensive care unit.

Twenty consecutive admissions to an 8-bed general adult intensive care unit over a 2-yr period mean age 62.9 yr (range 24–86) included 17 males and 3 females with a diagnosis of post-cardio-respiratory arrest were studied. All patients were receiving mechanical ventilation and had an arterial line and a pulmonary artery catheter inserted on admission.

Serial arterial blood gases and cardiac output measurements taken were reviewed for the first 24 h of admission from the case notes. The number of measurements recorded ranged from four to nine arterial gas samples over the 24 h. The cardiac output was measured using thermodilution with 10 ml of cold saline. All the data were collected from measurements taken within 20 min of each other. Linear regression analysis demonstrated no consistent relationship between the calculated base deficit and cardiac index ($r = 0.02$, $P = 0.82$) when data were pooled for the study group. In four of the study group however, there appeared to be a good relationship ($r = -0.78$, $r = -0.76$, $r = -0.82$, $r = 0.79$, $P<0.05$) but this was not reflective of the overall trend (Table 23). Three patients showed a strong negative correlation that is as the cardiac index decreased the base deficit increased and one the opposite trend.

Table 23 Pearson's correlation for cardiac index and calculated base deficit *$P<0.05$

Patient	1	2	3	4	5	6	7	8	9	10
Pearson's r	−0.56	0.73	0.02	0.62	−0.82*	−0.56	−0.47	0.07	0.13	−0.78*
Samples	9	7	4	4	8	5	8	7	8	7
Patient	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Pearson's r	−0.67	−0.69	0.79*	−0.76*	0.23	0.44	0.24	0.18	0.09	0.48
Samples	4	7	7	9	7	7	7	8	5	7

Our data suggest that the calculated base deficit is a poor predictor of the cardiac index in post cardiac arrest patients. We recommend that the base deficit should be applied with caution in the clinical assessment of cardiac output.

Keywords: acid–base equilibrium; complications, arrest, cardiac;

Calibration of LOD scoring in a high mortality population

D. A. Sperry and **J. Eddleston**

Intensive Care Unit, Manchester Royal Infirmary, Oxford Road, Manchester, UK

The population of the North West suffers higher comorbidity rates than that of England as a whole. Standardized mortality ratios for ischaemic heart disease (1.2), cerebrovascular disease (1.16) and chronic obstructive airways disease (1.4) are all significantly higher than the national average.[1]

Nine intensive care units based in the North West provided data on admissions and outcomes from the beginning of 1997. After exclusion of cardiac surgery, burns patients, patients under 18 and those with significant missing data 3393 records were included in a local database. Logistic organ dysfunction (LOD) scores were calculated as described by LeGall.[2]

Compared with the European/American ENAS database patient age (mean 57.5, median 60, SD 21) was similar (mean 57.2, SD 18) but there were differences in the distribution of organ dysfunction, proportion of elective patients admitted and mortality (0.39 *vs* 0.22).

Calibration of LOD scores to the model, determined from the Hosmer-Lemeshow statistics C and H, was poor ($C = 653$, $P<0.001$; $H = 674$, $P<0.001$) due to higher than expected observed mortality for a given organ severity. The area under the receiver operating curve (ROC), a measure the test's ability to discriminate, was lower than originally described (0.72 *vs* 0.85). Customization of the score for the North West database was performed using the method described by Zhu.[3] First level customization of the logit failed ($C = 27$, $P<0.01$, $H = 15.2$, $P = 0.13$), but second level customization of the coefficients calibrated successfully ($C = 11.1$, $P = 0.35$, $H = 10.3$, $P = 0.41$). Area under the ROC was 0.82. Higher weightings were obtained for all cardiovascular variables with an increase in predicted mortality over the original LOD score for 3215 patients (95%).

The customized score was then applied in a further model to determine the effect of hospital transfer prior to intensive care on weighted mortality. A total of 838 patients (24.7%) patients were transferred. Overall relative risk of dying in intensive care was 1.13 (OR 1.22, 95% CI 1.04–1.43). Allowing for customized organ severity and patient age transfer contributed significant excess mortality ($P<0.005$).

Calibrated scoring systems allow local analysis of contributing factors in patient mortality, whilst controlling for illness severity

Keywords: complications, morbidity; intensive care, audit

References

1 NW Regional Health Authority Comparative Vital Statistics 1990 Information Analysis dept. NWRHA
2 Le Gall J-R, Klar J, Lemeshow S *et al.* *JAMA* 1996, **276**: 802–10
3 Zhu BP, Lemeshow S, Hosmer DW *et al.* *Crit Care Med 1996*; 24: 57–63

Haematological malignancy in ICU

S. Bianchi, D. Sperry, J. Benson and J. Eddleston

Intensive Care Unit, Manchester Royal Infirmary, Oxford Road, Manchester M13, UK

The admission of patients suffering haematological malignancy to the intensive care unit (ICU) is controversial due to their poor prognosis. The dilemma regarding admission has escalated with the development of more aggressive forms of chemotherapy. Whilst improving survival from primary disease these treatments also result in an increase in life-threatening complications requiring ICU admission.[1] Analysis of patients admitted to a large ICU over a 3-yr period and data collected from surrounding regional hospitals has allowed determination of various prognostic factors that may assist in patient management.

A retrospective observational study on patients with haematological malignancy admitted to ICU between January 1996 and July 1999 was conducted. Patients admitted from medical and haematological wards and a regional cancer centre were included, as were data from regional ICUs. Data included malignancy type, reason for admission, severity and duration of leucopenia, creatinine on admission, Logistic Organ Dysfunction (LOD) score, requirement for invasive ventilation and survival.

Sixteen patients (8 male, 8 female) were admitted to the ICU within the specified time. An additional 13 patients were admitted to regional ICUs between January 1997 and July 1999. Haematological diagnoses: Hodgkin's lymphoma (7), non-Hodgkin's lymphoma (1), chronical lymphocytic leukaemia (3), chronic myeloid leukaemia (6), acute myelogenous leukaemia (6), acute lymphoblastic leukaemia (3), multiple myeloma (2). Admission to ICU was precipitated by pneumonia (35%), adult respiratory distress syndrome (15%), sepsis (15%), multi-organ failure (15%), bleeding (12%) and graft-versus-host disease (8%). On admission LOD scores ranged from 1–16 (average 6.5) and ICU mortality was 71% Of the 30% surviving ICU, only 18% survived to long term (>6 months). Survival was associated with not requiring mechanical ventilation, a normal white cell count or brief period of neutropenia. A creatinine on admission of greater than 200 μmol litre^{-1} was noted to be associated with mortality ($P = 0.05$). In logistic regression analysis haematological malignancy is significantly associated with in hospital mortality ($P<0.005$). This association is strengthened when age is taken into account ($P<0.001$), but is not significant when organ severity is controlled for ($P = 0.10$). Relative risk of in hospital death for patients with haematological malignancy admitted to ICU was 1.9 (OR 4.36 95%CI 1.6–12.1). These results suggest that patients with haematological malignancy are admitted to ICU with more severe illness than matched patients with other underlying disease.

In conclusion it can be shown that a high mortality is associated with admission of such patients to ICU. Prognosis is guided by several factors including the requirement for mechanical ventilation,[2] LOD score >10 and severe prolonged neutropenia. Improved prognosis is associated with normal white cell count, rapid recovery of bone marow[3], normal admission creatinine and avoidance of mechanical ventilation.

Keywords: intensive care, audit; cancer

References

1 Faria F, Alves P. *Crit Care* 1999; **3** (suppl 1): 238
2 Lloyd-Thomas AR. *Intensive Care Med* 1996; **12**: 317–24
3 Ben-Abraham R, Segal E, Hardan I, *et al.* *Harefuah* 1997; **133**: 91–4, 167

Correlation of TISS and Nurse Dependency scores with the pilot version of the SOPRA score

R. Vaja, P. Spiers and S. Gulley

Intensive Care Unit, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK

A number of severity of illness scoring systems have been developed and are widely used in intensive care practice. The Therapeutic Intervention Scoring System (TISS) is used as a tool for assessing severity of illness, therapeutic and nursing manpower requirements as well as cost-benefit analysis.[1] TISS uses over 70 variables, however it does not take into account non-interventional demands on time such as communications and support for relatives. The Lincolnshire demand model for Nurse Dependency (ND) adapted from an earlier model[2] is used in our ICU, scoring 1, 2 or 3 with increasing dependence.

The Intensive Care National Audit and Research Centre (ICNARC) Working Group released a pilot version of their System of Patient Related Activities (SOPRA) at the Riverside/ICS Meeting in December 1998. SOPRA is intended to indicate the degree of care necessary when treating a critically ill patient. In one score it is hoped to assess the intensity of impact each patient made on the work of the ICU that day.

The aim of this study was to test for any association between TISS, SOPRA and ND scores. Daily TISS, SOPRA and ND scores were recorded over a period of 2 months on all patients on our ICU. The results were analysed using non-parametric tests, Spearman's correlation and linear regression methods.

We recorded 488 scores for each system (Table 24). Median SOPRA score was 25 (range 12–60), that of TISS was 34 (11–73). There was no correlation between SOPRA and ND scores ($r^2 = 0.18$). There was no correlation between TISS and ND ($r^2 = 0.14$). Despite many similarities between SOPRA and TISS their correlation was poor ($r^2 = 0.49$)

Our nursing staff found the SOPRA score more specific and less subjective than TISS. It was also felt to be more representative of current Intensive Care practice.

We conclude that the SOPRA and TISS are significantly different scoring systems despite having many common factors. However

Table 24 Median and range of scores Correlation of SOPRA to TISS and ND

			Correlation to SOPRA			
	n	Median (range)	r	95% CI	r^2	P
SOPRA	488	25 (12–60)				
TISS	488	34 (11–73)	0.67	0.61–0.71	0.49	<0.0001
ND	488	3 (1–3)	0.49	0.42–0.55	0.18	<0.0001

further evaluation is required to identify any advantage SOPRA may offer over TISS.

Keywords: intensive care, audit

References

1 Keene AR, Cullen D. *Crit Care Med* 1983; **11**: 1–3

2 Ball J, Oreschnick R. *Senior Nurse* 1986; **4**: 27–29

An audit of pre-operative optimization Derriford Hospital

S. P. Courtman and M B. Walker

Department of Anaesthesia, Derriford Hospital, Plymouth, Devon PL6 8DH, UK

Pre-operative optimization (PO) has been shown to reduce mortality, duration of hospital stay and hospital costs.[1] [2] The Intensive Care National Audit and Research Centre (ICNARC) data base shows that 3.4% of all patients are admitted for PO in contrast to 1.9% at our centre. The effective provision of PO requires a bed on the intensive care unit (ICU)–high dependency unit (HDU) with appropriate levels of staffing. There are suggested guidelines for identifying the high-risk surgical population based on surgical categories, underlying medical conditions and HDU admission criteria. At Plymouth there is a nine-bedded ICU and a four-bedded HDU which admit 1200 patients per year, of which, 58% are surgical cases.

We performed a prospective audit of 100 consecutive surgical admissions to ICU–HDU assessing whether current resources are sufficient to provide PO. Demographic data were collected and the surgical category noted. The availability of a bed in the 3 h preceding surgery for each admission was recorded. Pre-operative clinical and biochemical data were collected from the notes in accordance with admission criteria used in previous studies. The APACHE II scores, diagnostic and outcome data were obtained using the ICNARC database.

The majority of patients underwent vascular or abdominal surgery (laparotomy $n = 40$, vascular $n = 26$, orthopaedics $n = 13$, other $n = 21$). A bed was available pre-operatively for all booked admissions ($n = 26$). Of the remaining non-booked admissions ($n = 74$), 61% had a bed available for PO without transferring a patient off ICU/HDU. Two patients were admitted specifically for PO. There was no difference in APACHE II scores or outcome between booked and non-booked cases.

Eight patients were identified who required admission by recognized criteria. However, data were rarely complete with certain variables seldom recorded (respiratory rate 13%, urine output 15%, temperature 72%, blood gases 11%). Only nine patients had complete basic observations documented in the notes and more patients might have satisfied the criteria if documentation was complete.

The low frequency of PO and availability of beds indicates that we should be aiming to increase the number of patients admitted pre-operatively. The ICNARC data for the subgroup of elective vascular case clearly illustrates this (10.2% *vs* 2.5% Derriford). This audit demonstrates the difficulty in identifying high-risk surgical patients. Poor data collection is a major contributor. A dramatic change in ward care and use of single referral criteria would improve this.

Keywords: intensive care, audit

References

1 Wilson J, Woods I, Fawcett J, *et al. BMJ* 1999; **318**: 1099–103

2 Guest JF, Boyd O, Hart WM, Bennet ED. *Intensive Care Med* 1997; **23**: 85–90

Peripherally inserted central venous catheters (PICC)

N. Mehta, S. Nadel, A Reeve, A. Nadel and J. Britto

PICU, St. Mary's Hospital, London W2 1NY, UK

Venepuncture and repeated peripheral venous cannulations are the most frequently performed painful procedures in hospitalized children, resulting in an unpleasant experience for both the child and parents.[1] Peripheral cannulae are short lasting, easily dislodged and can be difficult to maintain. On the other hand, tunnelled catheters are invasive, require specialized expertise and may be associated with significant risks and costs.[2]

Aim: To evaluate the role of peripherally inserted central venous catheters (PICC) for intermediate term venous access in hospitalized children.

Methods: A prospective descriptive study, evaluating insertion of PICC in hospitalised children requiring venous access for intermediate term (7 days to 2 months). Silicon catheters were inserted in the antecubital fossa under strict aseptic conditions using a modified Seldinger technique under appropriate sedation and analgesia.[3] Pain experienced during insertions, was quantified using validated pain scales.[4] During the course of the study, a sample of children ($n = 55$) requiring peripheral venous cannulation (PVC) was also studied as a cohort for comparison of pain experienced during the procedures.

Results: PICC insertion was attempted in 90 patients (median age 4 years; range 8 days – 16 yr) over a period of 18 months, between October 1997 and April 1999 with a success rate of 92%. Median time for procedure was 45 min (range 15–210). Median pain scores as assessed by nurses and parent/child were 1 (1– 5) and 2 (0–4) respectively. Therapy was completed in 75 (83%) patients with PICC. Fifteen PICC were prematurely removed Median length of time *in situ* was 10 days, a total of 1081 catheter days. There were no cases of clinically detectable thrombotic complications or PICC related sepsis. Coagulase-negative staphylococci were grown from 8/90 (9%) catheter tips. PICC were used for intravenous antimicrobials, total parenteral nutrition, blood transfusions, erythropoetin and blood sampling ($n = 529$). In addition, 55 patients (median age 2 years; range 10 days – 17 yr) subjected to peripheral venous cannulations (PVC) were also evaluated. Median time for procedure was 10 min (1–60) with median pain scores of 2 (1– 5) and 3 (0–4) by nurses and parent/child respectively.

Conclusions: PICC provide an effective alternative to repeated peripheral venous cannulations and can be inserted by designated trained medical and nursing team with a high success rate. PICC are long lasting, better tolerated, allow repeated blood sampling, have few complications and may facilitate home care for some patients. PICC should be the vascular access of choice for adults and children requiring intermediate-term vascular access and intensivists have a role in setting up and providing this service in the UK.

Keywords: veins, cannulation; children

References

1 British Paediatric Association Working Party. *The Prevention and Control of Pain in Children. A Manual for Health Professionals*. London: BPA, 1996

2 Bruckner JC, Forster A, Gamulin Z, *et al. Anaesthesia* 1986; 41: 408–12

3 Mehta N, Reeve A, Britto J. How To Guide· PICC in children. *Care of the Critically Ill*, Centre Insert, August 1999, Volume 15 4

4 Carter B. *Child and Infant Pain. The Principles of Nursing Care and Management*. 1994; Chapter 3

Table 25 Features and outcome of five patients admitted to ICU with haemophagocytic lymphohistiocytosis (HLH)

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	2 yr 2 months	4 yr 4 months	4 yr 9 months	2 months 20 days	1 month
Sex	Female	Male	Male	Female	Male
Diagnosis on admission	Cellulitis	Dental sepsis	Sepsis	Sepsis	Sepsis
Liver function	Deranged	Deranged	Deranged	Deranged	Failure
Bone marrow	Thrombocytopaenia	Anaemia	Neutropaenia	Pancytopaenia	Anaemia
Metabolic acidosis	Absent	Mild	Moderate	Severe	Severe
Haemophagocytosis	Liver, spleen	Bone marrow	Bone marrow	Bone marrow	Liver
Outcome in PICU	Died	Discharged	Discharged	Died	Died

Haemophagocytic lymphohistiocytosis (HLH) on the intensive care unit

N. Mehta, S. Nadel, M. Levin and J. Britto

PICU, St. Mary's Hospital, London W2 1NY, UK

HLH is a rare disorder characterised by proliferation of cells of the mononuclear phagocyte system (histiocytes). It comprises a primary (inherited) or familial form and a secondary or acquired (usually infection associated) syndrome. Both forms of the disease may be commonly fatal if not treated with specific therapy. The familial form of the disease is commonest in the first few years of life. Secondary HLH can be found in all ages and diagnosis is based on clinical, laboratory and histopathological criteria. We report five cases of HLH admitted to our PICU to highlight some of the presenting features and outcomes (Table 25).

In our series of cases of HLH, three of the five cases were admitted as multiorgan failure following suspected sepsis. Metabolic acidosis, which was resistant to correction, was a common feature. The other two cases were admitted with focal infections who then developed full-blown multisystem involvement. Diagnosis was confirmed in four of the five cases after admission to the PICU, on the basis of characteristic histopathology on organ biopsies.[1] Clinical features consistent with HLH included fever, organomegaly, cytopaenias, disseminated intravascular coagulation, liver cell failure, hyperlipidaemia and acidosis. These patients required intensive care for supportive therapy for multisystem failure. Bone marrow, liver and lymph node biopsies confirmed the diagnosis in three cases during their illness.

HLH is rare but fatal if not treated. Early diagnosis with specific investigations may provide an opportunity for appropriate therapy. Intensivists should be aware of the presentation of HLH in ICU setting especially masquerading as sepsis with multiorgan failure and every effort should be made to diagnose the condition with the help of bone marrow examination and histopathology. HLH continues to be a highly underdiagnosed condition both in paediatric and adult ICU settings.

Keywords: blood, lymphocytes; intensive care

Reference

1 Henter J-I, Elinder G, Ost A, *et al. Semin Oncol* 1991; **18**: 29–33

Implementation of evidence base into clinical practice in UK intensive care units

B. H. Cuthbertson, S. A. Stott and N. R. Webster

Academic Unit of Anaesthesia and Intensive Care, University of Aberdeen, Aberdeen AB25 2ZD, UK

Inhaled nitric oxide has been used in UK clinical practice for a number of years and was widely used in the management of ARDS despite the lack of available evidence of benefit to support this practice. Current practice was surveyed in 1996 and this lead to the development of clinical practice guidelines based on best available evidence and was intended to encourage safe practice whilst awaiting evidence of benefit.[1] Randomized controlled trials regarding the use of inhaled nitric oxide in ARDS followed providing an ideal opportunity to study the implementation of clinical guidelines based on evolving evidence.

We surveyed the respondents to our previous survey and asked questions regarding current clinical use of inhaled nitric oxide, knowledge and views on the UK guidelines for inhaled nitric oxide treatment and knowledge and views of current evidence.

We received a 60% reply rate from 50 questionnaires. Of these, 76% stated that they still used inhaled nitric oxide. Ninety-one per cent of respondents still used inhaled nitric oxide for ARDS and 54% for other indications. In terms of severity of ARDS, only 36% followed UK guidelines. Regarding dosage, monitoring and delivery, all units administered inhaled nitric oxide according to the guidelines with the exception of scavenging and methaemoglobin measurement. Many units stated that inhaled nitric oxide was only being used for severe ARDS which was non-responsive to conventional therapies. A similar number of patients had received inhaled nitric oxide this year as in 1996. The vast majority of units (86%) were aware of the UK guidelines but only 62% followed them and 71% felt that production of guidelines was appropriate. Of the units still using inhaled nitric oxide, 14% were not aware of the two major randomized trials that gave evidence on the use of inhaled nitric oxide in ARDS. Of the units that were aware of these studies, 64% of units felt that the results were either equivocal or not supportive of the use of inhaled nitric oxide in ARDS. Fifty per cent of these units continued to use inhaled nitric oxide. The majority of units (80%) felt that further evidence was required and only 28% felt that inhaled nitric oxide should no longer be used in the management of ARDS. All surveyed units also used other unproven therapies in the management of ARDS.

Inhaled nitric oxide is still widely used in adult ICUs predominantly in line with UK guidelines. Encouragingly, most users were aware of UK guidelines for inhaled nitric oxide in adult ICU and claimed to follow them. Over 70% felt that clinical practice guidelines were appropriate to allow the safe use of an unlicensed therapy. This suggests that consensus guidelines could be put to use in other areas of clinical practice. Most units are aware of the major studies of inhaled nitric oxide in ARDS and the majority believe that the evidence does not support its use. Despite this, use of this therapy continues. This is not unique to the use of nitric oxide since other unproven therapies are used in the management of ARDS. This suggests that much of current clinical practice is not evidence based.

Keywords. intensive care; pharmacology, nitric oxide

Reference

1 Cuthbertson BH, Dellinger P, Dyar OJ, *et al Intensive Care Med* 1997; **23**: 1212–18

A comparison of bispectral index with Ramsay sedation score in patients sedated with dexmedetomidine in the ICU

R. M. Venn, R. J Cusack, A. Rhodes, P J Newman and R. M Grounds

Department of Intensive Care, St George's Hospital, Blackshaw Road, London SW17 OQT, UK

Assessment of the depth of sedation in ICU patients is important if the deleterious consequences of over- or under-sedation are to be avoided. The Ramsay sedation score (RSS) whilst being easy to use, is very subjective in nature and neuromuscular paralysis makes interpretation difficult. Measurement of sedation utilizing the bispectral index (BIS), a novel and easily interpretatable, processed EEG, overcomes these problems, and its use has been explored in the ICU setting.[1] BIS has previously been shown to correlate with the modified RSS.[2] Dexmedetomidine, a highly selective alpha 2 agonist, is being investigated for sedation in the ICU, and we have studied its effects on BIS and correlated this with the RSS in the ICU.

Following approval of the LREC, six medical patients (mean APACHE II score 23, range 20–26) requiring ventilation in the ICU, received a dexmedetomidine infusion (0.2–2.5 mcg kg^{-1} h^{-1}) for up to 24 h and depth of sedation was assessed using RSS. BIS was continuously monitored on Aspect A-2000 with the sensor placed in a fronto-temporal montage. Hourly RSS were recorded and corresponding BIS measurements averaged over 1 min. ANOVA with Newman-Keuls post test analysis for repeated observations and linear regression analysis were used for statistical comparison. $P<0.05$ was considered statistically significant.

BIS can be usefully used to monitor the depth of sedation with dexmedetomidine in the ICU (Table 26), as has been shown previously with other agents.[2] BIS can be classified into a low, middle and high range corresponding to RSS of 1&2, 3&4, 5&6, when dexmedetomidine is used as the sole sedation agent in critically ill patients.

Keywords: intensive care, sedation; sedation

Acknowledgement

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References

1 De Deyne C, Struys M, Decruyenaere J, *et al. Intensive Care Med* 1998; **24**: 1294–8

2 Shah N, Clack S, Chea F, *et al. Anesthesiology* 1996; **85**: A469

Table 26 Correlation of depth of sedation following dexmedetomidine as measured by Ramsay score (RSS) and bispectral index (BIS) Linear regression analysis for RSS *vs* BIS gave $R^2 = 0.93$

No. of observations	RSS	BIS (mean (SD))	Significance
4	1	94.5 (2.4)	
4	2	84.8 (4.6)	
21	3	60.0 (23.7)	$P<0.1$ *vs* RSS 1, $P<0.05$ *vs* RSS 2
49	4	61.2 (20.6)	$P<0.001$ *vs* RSS 5 and 6
56	5	47.7 (14.2)	
20	6	42.4 (17.3)	

Chest drainage: clinical evaluation of a Seldinger drainage kit

C. Patel, **A. C. Beaumont** and J C. Banks

Department of Intensive Care, Kent and Canterbury Hospital, Canterbury, Kent CT1 3NG, UK

Chest drain insertion is required in the intensive care unit and high dependency care setting. Catheter insertion may be required for pneumothorax both spontaneous and iatrogenic, for the drainage of pleural effusions, or for the drainage of empyemas. Large bore catheters are difficult to insert and may be associated with adverse complications.[1] A new catheter system developed by SIMS Portex has been introduced to insert a small catheter into the chest. This has been developed to minimise the complications associated with conventional tube drainage. The catheter is inserted over a guide wire with dilation of the chest wall. The catheter is 285 mm long has two lateral eyes and an open end.

Data are presented on 20 small-bore (12 French gauge) Seldinger chest drainage catheters. Three were placed in children two with spontaneous pneumothorax (10 and 15 yr) and one with parapneumonic effusion (7 yr). Seventeen further catheters were placed in adults: seven for pneumothoraces and 10 for effusions. Four catheters were inserted as emergencies for deteriorating respiratory function. These patients were all being ventilated on the intensive care unit.

All catheters were inserted with ease into the pleural space. Ultrasound guidance for effusions to assess the presence of loculations, or X-ray diagnosis of the pneumothorax prior to catheter insertion was used for all cases. One catheter system needed to be removed due to apparent blockage All the other catheters performed well draining an average of 2.1 litre of fluid for the effusions and reinflating the lung in all the patients with pneumothoraces.

Small-bore catheter chest drainage is simple and effective [2] The use of a guide wire system has advantages over conventional open chest drain insertion. There is less possibility of damage to the underlying lung tissue, less probability of the introduction of air into the thoracic cavity and greater operator confidence. The catheter is more comfortable, easier to insert, and effective in clinical use. This study confirms that small catheters are effective for emergency and non-emergency pneumothorax and effusion drainage.[3]

Keywords: equipment, catheters

References

1 Hyde J, Sykes T, Graham T *BMJ* 1997; **314**: 914–5

2 Grodzin CJ, Balk RA. *Chest* 1997; **111**: 981–8

3 Conces DJ, Tarver RD, Gray WC, *et al. Chest* 1988; **94**: 55–7

An assessment of attitudes to pulmonary artery flotation catheters in the United Kingdom and Ireland

R. Greer and J. Benson

Intensive Care Unit, Manchester Royal Infirmary, Oxford Road, Manchester M20 2UZ, UK

There is concern over the safety of the use of pulmonary artery flotation catheters (PAFC) in the United Kingdom.[1] We were unable to find any data directly applicable to practice in the United Kingdom and Ireland. The aim of our study was to assess the practice in this country by the use of a telephone questionnaire. A standardised questionnaire was used and answered by senior

Table 27 Indications for placing a PAFC

Indicator	Incidence
ARDS	91%
Sepsis	85%
Use of inotropes	73%
Nitric oxide therapy	67%
Pulmonary hypertension	58%
Eclampsia	46%
Raised intracranial pressure	12%
Renal support	8%

medical personnel. We phoned 48 intensive care units who had more than 8 beds and we stipulated that the answers reflected practice in the unit.

We found that a trainee routinely passes the pulmonary artery flotation catheter however the decision to pass a PAFC was only made by a consultant in 30% of cases. In more than 80% of intensive care units less than 40% of patients had a PAFC *in situ*. The incidence of indications for placing a PAFC are sited in Table 27.

In the intensive care units in our survey the main forms of measurement of cardiac output were cold injectate (77%), continuous thermodilution (48%), echocardiography and Doppler methods (4%), and thoracic bioimpedance (2%).

In over 90% of cases the measurements routinely taken with the PAFC were pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, central venous pressure and systemic vascular resistance. Oxygen delivery (48%), oxygen consumption (40%), mixed venous saturation (50%) and right and left stroke work index (<35%) were less frequently recorded.

Our data suggest that in only 20% of the units we studied was a pulmonary artery flotation catheter routinely used. In addition it appears that not all clinicians in the United Kingdom and Ireland feel that a PAFC is indicated in a number of well documented clinical situations.

Keywords: equipment, catheters

Reference

1 Soni N. *BMJ* 1996; **313**: 763–4

A simple method for calculating the required size of a high dependency unit

O. A. Williams, J. A. Grabham[1], P. P Musto and D. G. Raitt

Directorates of Anaesthesia and [1]Surgery, Leicester General Hospital NHS Trust, Gwendolen Road, Leicester LE5 4PW, UK

As part of a business plan for the establishment of a high dependency unit (HDU) in a 742 bedded acute teaching hospital, a study was carried out to establish the number of beds required. The hospital already had a six-bed intensive care unit (ICU), with a seventh bed staffed part-time to provide postoperative care for elective surgical cases. Over a 2-week period, one investigator (JAG) visited each of 16 acute wards daily, to identify patients appropriate for HDU admission. He also visited the ICU to identify any patients for whom HDU would provide a step-down facility, and examined operating theatre recovery records to identify any patients who could not be returned to the general ward within 3 h following their surgery.

At each visit, the nurse in charge was asked to identify any patients requiring additional nursing care or in need of increased monitoring. Each patient was assessed using the Therapeutic Intervention Scoring System (TISS).[1] A score of greater than 10 indicated suitability for HDU admission. Physiological and biochemical data were also collected to allow calculation of each patient's Simplified Acute Physiology Score (SAPS II)[2] and hence calculation of predicted mortality.

During the 14 day period, 35 patients were identified as requiring additional care. Their mean TISS score was 14.1 (range 10–33) and their mean predicted mortality was 5.7% (0–19.6%). Each patient had a predicted average HDU stay of 2.2 days (1–5 days) to give a total of 76 patient days. The occupancy of the proposed HDU ranged from 3 to 8 patients per day with a mean of 5.4 per day, suggesting that an HDU containing a minimum of six beds would be appropriate to serve the needs of the hospital.

Keywords: intensive care, audit

References

1 Keene AR, Cullen DJ. *Crit Care Med* 1983; **11**: 1–3
2 Le Gall J-R, Lemeshow S, Saulnier F. *JAMA* 1993; **270**: 2957–63

Heart rate variability displays 1/*f* noise in critical illness and correlates with severity of multiple organ dysfunction

S. Tibby[1,2], H Frndova[1] and P Cox[1]

[1]Hospital for Sick Children, 555 University Ave, Toronto, M5G, Canada
[2]Guy's Hospital, London, UK

It has been postulated that multiple organ dysfunction (MOD) results from an uncoupling of connections between organs, which can be viewed as biological oscillators, with subsequent loss of 'complex' or adaptive behaviour of the body as a whole. If so, this process may be demonstrated by loss of variability in individual organs. To test this hypothesis, we measured heart rate variability (HRV) in a cross section of ICU patients, using a non-linear model based on variations occurring in many complex naturally occurring systems. These variations obey a power law (known as 1/*f* noise) when plotted as frequency distributions with log–log axes. The power relationship is such that $aE^b = f$, where E is the amount of variation, f is the frequency of observations, and b and log (a) refer to the slope and intercept, respectively. We postulated that increasing MOD would be associated with loss of HRV.

A 5-min, real-time ECG recording was downloaded to a personal computer at a sample frequency of 500 Hz utilizing an analogue to digital data translation board. Instantaneous heart rate was calculated for each RR interval, artefact screened and excluded using a Poincaré plot, and the mean heart rate was calculated. Absolute variations from the mean were plotted on a 20-bin histogram, and from this a frequency distribution was plotted in log10–log10 space, producing a unique regression line for each measurement. Patients were grouped according to number of organs failing (0–1, 2, ≥3) along the lines of mortality risk.

A total of 109 measurements, made on 52 children, median age 7 months (range 2 days to 16 yr) were spread across organ failure groups such that: 0–1 organ failures ($n = 56$), 2 ($n = 32$), and ≥3 ($n = 21$) (Figure 2). Breakdown of individual organ failures gave: respiratory ($n = 67$), cardiac ($n = 48$), haematologic ($n = 19$), liver ($n = 16$), renal ($n = 13$), neurologic ($n = 7$). Regression analysis gave an overall mean (SD) r^2 of 0.87 (0.09), with no difference between organ failure groups ($P = 0.46$). The mean (SD) slope for all patients was −1.80 (0.29), and again was similar regardless of the degree of MOD ($P = 0.24$). The three groups showed significant differences for both the x- and y-intercepts, with decreasing HRV (i.e. left-shifted regression lines with decreasing intercept) seen amongst those with greatest MOD (ANOVA $P<0.001$ for all groups). A multiple regression model showed

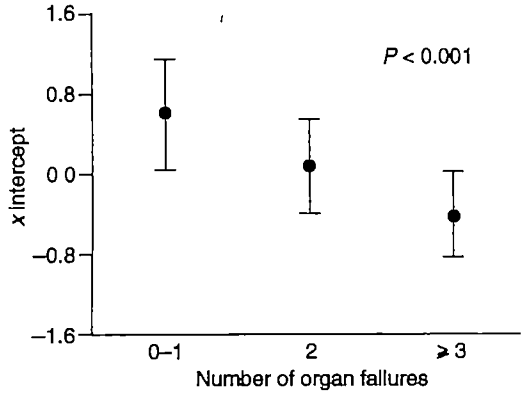

Fig 2 Heart rate variability in patients with varying numbers of organ failures.

this to be independent of the potential confounding factors: inotrope, opiate or benzodiazepine use.

(1) HRV exhibits $1/f$ noise, as shown by the high r^2 value, and consistency of slope.
(2) HRV can be quantified by change in intercept of the regression line.
(3) Loss of HRV (evidenced by a left-shifted regression line) is seen with increasing MOD.
(4) This effect appears to be independent of inotrope, opiate or benzodiazepine use.
(5) These findings are consistent with MOD representing an uncoupling of inter-organ communication, and this model may be used as a marker for disease severity.

Keywords: heart, heart rate

Surfactant supplementation in respiratory syncytial virus bronchiolitis

S. M. Tibby[1], M Hatherill[1], S M. Wright[2], P. Wilson[1], A. D. Postle[2] and I. A. Murdoch[1]

[1]*Guy's Hospital, Saint Thomas Street, London SE1 9RT, UK.*
[2]*Southampton General Hospital, Southampton, UK*

Infants with respiratory syncytial virus (RSV) bronchiolitis are deficient in surfactant, both in quantity and ability to reduce surface tension. Evidence also suggests surfactant has a role in maintaining the patency of conducting airways which has implications for RSV bronchiolitis. A randomized, controlled trial was undertaken to assess the effects of exogenous surfactant supplementation to RSV positive infants on pulmonary mechanics, indices of gas exchange, and the phospholipid composition of bronchoalveolar lavage fluid (BALF).

Nineteen ventilated infants (median corrected age 4 weeks) received either two doses of surfactant (Survanta, 100 mg kg^{-1}) within 24 and 48 h of mechanical ventilation ($n = 9$), or air placebo ($n = 10$). Lung mechanics were measured using the single breath occlusion technique, before dose, and at 1, 2 and 6 h after each dose. BALF were taken before the first dose, and 24 h after the second. Phospholipid profiles were measured by electrospray ionisation mass spectrometry. Statistical analysis employed 2-way, repeated measures ANOVA, with post hoc Bonferroni adjusted t-tests comparing time point 0 h (before treatment) and 30 h (6 h after second treatment).

Infants were well matched in terms of age, prematurity, chronic lung disease and severity of lung disease at enrolment. Static lung compliance and resistance of infants in the placebo but not in the surfactant-treated group became progressively worse over the first 30 h following enrolment (Table 28).

Table 28 Static lung compliance and resistance of ventilated infants

		0 h	30 h	Bonferroni P
Compliance (ml cm H_2O^{-1} kg^{-1})	Placebo	0.36	0.27	$P<0.01$
	Surfactant	0.40	0.37	$P = 0.4$
Resistance (cm H_2O $litre^{-1}$ s^{-1})	Placebo	229	391	$P<0.001$
	Surfactant	253	226	$P = 0.9$

Surfactant-treated infants showed a more rapid improvement in oxygenation and ventilation indices and alveolar-arterial gradient over the first 60 h of mechanical ventilation. Surfactant status was assessed from the concentration ratio in BALF of the disaturated phospholipid species dipalmitoylphosphatidylcholine to that of the monounsaturated species palmitoyloleoylphosphatidylcholine. This ratio correlated with both lung compliance ($r = 0.53$, $P = 0.02$) and resistance ($r = -0.50$, $P = 0.03$), and over time increased in the treated group and declined in placebo infants.

These data suggest that functional surfactant has a role in maintaining small airway patency in RSV infected infants and supplementation has the potential to reduce length of ventilation and barotrauma.

Keywords: infection, viral; lung, surfactant

Is pre-optimization of patients undergoing major surgery justified?

R. G. Rowlands and A. Beaumont

Kent and Canterbury Hospital, Ethelbert Road, Canterbury, Kent CT1 3NG, UK

Wilson and colleagues[1] recently published a randomized, controlled, trial focusing on the pre-optimization of high risk surgical patients undergoing major surgical procedures which appeared to show a clear benefit in preoperative intervention versus control in terms of reducing mortality, morbidity and hospital stay. Our remit was to conduct a prospective audit, utilizing POSSUM (physiological and operative severity score for the enumeration of mortality and morbidity)[2] analysis, to ascertain whether the actual risks of mortality and morbidity would match those expected in a similar control group of patients at Kent and Canterbury Hospital.

Between May 17 and July 5, 1999, 33 consecutive elective patients undergoing major surgery, as defined by POSSUM, were identified and followed up until discharged from hospital. All patients received routine anaesthetic and postoperative care and 12 were admitted to intensive care postoperatively.

Median predicted risks of mortality and morbidity were calculated using the POSSUM scoring system and these values compared favourably with those predicted of the control group in the York study (Table 29). In addition the median ages of the patients in the study were similar as were the range of operations conducted. Actual risks of mortality and morbidity were significantly lower than the expected risks calculated and also lower than the York control group.

The high mortality of the York control group would seem to exaggerate the perceived benefit of pre-optimization when compared with the treatment group. Our study shows that a relatively low risk of mortality can be achieved with standard practices and would cast doubt on the need to subject whole surgical populations to vigorous pre-optimization therapy with the

Table 29 Mortality and morbidity data for patients receiving standard post-operative care at Kent and Canterbury Hospital compared with control group at York District Hospital

	K and C	York[1]
Age	70	71.5
Risk of mortality (%)		
Predicted	11.7	13.8
Actual	6.0	17.0
Risk of morbidity (%)		
Predicted	49.3	57.0
Actual	42.4	61.0

massive additional investment in intensive care services that would be needed

Keywords: intensive care, audit

References

1 Wilson J, Woods I, Fawcett J *et al. BMJ* 1999; **318**: 1099–103
2 Copeland G, Jones D, Walters M. *Br J Surg* 1991; **78**: 356–60

Changes in intensive care admissions with an interval of 5 years: a case-matched comparison

A. Scase, D. R. Goldhill and A. Sumner

The Intensive Care Unit, the Royal London Hospital, London E1 1BB, UK

Severity scoring systems, such as the Acute Physiology and Chronic Health Evaluation II (APACHE II)[1], are used to predict the outcome of patients admitted to the intensive care unit (ICU). Despite improvements in knowledge, equipment and skills, there is little convincing evidence from standardised mortality ratios (SMR: predicted hospital mortality/observed hospital mortality) that intensive care outcome has improved over a period of time.[2] The inability to detect changes in ICU outcome over time may be a result of limitations in severity scoring methods,[3] or changes in patient characteristics and severity of illness. A case-matched study of ICU admissions over two separate time periods is one way of investigating this issue.

Data on ICU admissions with a diagnosis of isolated head injury, chronic obstructive airway disease (COAD) or asthma were extracted from the North Thames ICU database.[2] Where possible each admission in 1992/1993 was matched for diagnosis, age and sex with one admission 5 yr later in 1997/1998. Differences between the time periods were examined using the Wilcoxon test. A $P<0.05$ was taken to be significant.

A total of 350 admissions were matched. From each time period there were 52 matched patients with isolated head injury, 86 with COAD and 37 with asthma (Table 30). Average age was 52.6 (SD 18.9, range 17–85) and 62% were male.

No significant differences were found between selected matched patients admitted to ICU 5 years apart. The results suggest that there have been no marked changes in either the patient population or outcome over this time period.

Keywords: intensive care, audit

References

1 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. *Crit Care Med* 1985; **13**: 818–29
2 Goldhill DR, Sumner A *Crit Care Med* 1998; **26**: 1337–45
3 Goldhill DR, Withington PS. *Anaesthesia* 1998; **53**: 89–90

Selective decontamination of the digestive tract — current national practice

J. R. Nixon and M S Nielsen

General Intensive Care Unit, Southampton General Hospital, Southampton SO16 6YD, UK

The use of selective decontamination of the digestive tract (SDD) in the intensive care setting was first reported in 1984[1] and, since then, has been the subject of many further studies. Two large meta-analyses have been conducted[2 3] and have suggested that, used alone, the topical element of SDD reduces the incidence of nosocomial respiratory tract infections (NRTIs), but has no impact on mortality. When the systemic element is added, however, not only are NRTIs prevented, but mortality is also reduced. It was estimated that either six[2], or five[3] patients had to be treated to prevent one NRTI and 23 to prevent one death. This would appear to be a worthwhile effect and one which, in terms of supporting evidence, compares favourably with some interventions used commonly in clinical practice. Despite this, there is an impression that SDD is very little used in this country and this study sought to explore this.

In September 1998, a questionnaire was sent to the directors of all general intensive care units (ICUs) in the UK and Ireland (n = 289). In addition to basic information about the unit, it asked whether SDD was in routine use, if so whether both topical and

Table 30 Comparison of matched ICU admissions in 1992/3 and 1997/8. GCS = Glasgow Coma Score, assumed normal (15) if unknown; ICU stay in days, APACHE II score, ROD = predicted risk of death from APACHE II

	Head injury		COAD		Asthma		All patients	
	92/93	97/98	92/93	97/98	92/93	97/98	92/93	97/98
GCS median	6	5	12	14	15	15	11	13
ICU stay								
average	3.6	4.6	10.4	8.7	5.9	4.0	7.4	6.5
median	2	2	5	4	2	2	3	3
APACHE II:								
average	14.6	15.7	21.7	21.1	15.4	13.1	18.2	17.8
SD	8.1	8.0	7.9	7.8	8.8	7.1	8.8	8.4
ROD.								
average	0.19	0.21	0.38	0.36	0.13	0.05	0.27	0.25
SD	0.15	0.20	0.24	0.24	0.23	0.06	0.24	0.23
% Deaths:								
ICU	15	19	26	28	5	3	18	20
hospital	21	22	40	42	5	5	27	28

systemic elements were used, and whether it was used on all or selected cases. If SDD was not routinely used, it asked for the reasons. A telephone follow-up of non-responders was undertaken.

Responses were obtained from 222 ICUs (77%). Of these, 66 were in teaching and 156 in non-teaching hospitals. A total of 213 units (96%) never used SDD. The nine units that did use it (six teaching, three non-teaching) did so only in selected cases. The commonest reason for selective use was major trauma, but liver failure, liver transplants, long-stay patients, burns and oesophageal perforation were also cited. Of the nine units using SDD, all but one used combined topical and systemic antibiotics. A lack of evidence of efficacy was the commonest reason for non-use (184 units) but concerns were also expressed about costs and cost-effectiveness (47 units) and the development of resistant organisms (35 units).

Unusually for intensive care practice, SDD represents a treatment for which there is reasonable evidence of efficacy and yet one which, paradoxically, is rarely used. It is particularly interesting that the lack of such evidence is most commonly cited as the reason for non-use. The potential for producing resistant organisms and the issue of cost-effectiveness are, as yet, unquantified and may prove to be more valid reasons.

Keyword: gastrointestinal tract

References

1 Stoutenbeek CP, van Saene HKF, Miranda DR, Zandstra DF *Intensive Care Med* 1984; **10**: 185–92
2 Selective Decontamination of the Digestive Tract Trialists' Collaborative Group. *BMJ* 1993, **307**: 525–32
3 D'Amico R, Pifferi S, Leonetti C, Torri V, Tinazzi A, Liberati A. *BMJ* 1998; **316**: 1275–85

Sequential organ scoring as a measure of effectiveness of critical care

C. Hutchinson, S. Craig and S. Ridley

Critical Care Complex, Norfolk and Norwich Acute NHS Trust, Brunswick Road, Norwich NR1 3SR, UK

Introduction: Our objective was to establish whether sequential organ scoring could be used on the intensive care unit (ICU) as a measure of effectiveness of care. There is no current data to support the assumption that intensive care is of benefit to patients and no established method of measurement. Randomized controlled trials are ethically and practically difficult to perform. In-hospital mortality is influenced by case-mix, and reflects institutional rather than specifically ICU performance.
Design: Observational non-randomized study of 100 consecutively admitted patients over a 5 month period between September 12, 1998 and February 12, 1999 whose duration of stay on the ICU exceeded 48 h.
Methods: Simple demographic data were collected (age, source and type of referral, diagnosis, premorbid condition). Organ dysfunction was assessed daily using the Logistic Organ Dysfunction System (LODS) as described by Le Gall[1] — measuring twelve physiological variables reflecting cardiovascular, respiratory, neurological, hepatic, renal and haematological status — using the worst physiological values for the preceding 24 h. Scores ranged from 0 (normal) to 22 (maximal derangement).
Main outcome measures: Change between score on admission and 72 h later, and comparison with eventual hospital mortality. The percentage of patients in whom there was no change or a decrease in organ score over this period.
Results: Seventy-five patients' stay exceeded 72 h. A decrease or no change in LODS score over this period was associated with eventual hospital survival. The specificity (true prediction of survival) was excellent (0.95). We were able to achieve no change or an improvement in organ dysfunction in 80% of our patients.

However, the ability to correctly predict death from a change in score was poor (sensitivity 0.36). In general, the change in score overestimated the chance of survival.

In terms of individual organ function, intensive care was able to consistently improve scores relating to the cardiovascular, respiratory and renal systems over the first 72 h of care, but not the neurological, hepatic or haematological systems.
Conclusions: The hallmark of modern intensive care is general organ support. Physiological improvement over the first 72 h of care is largely due to reversal of cardiovascular, respiratory and renal dysfunction. Daily organ scoring usefully reflects the ability of an intensive care unit to stabilise or reverse physiological dysfunction, and this has been shown to predict eventual survival. As a means of comparison between units, we suggest that a figure of 80% improvement or no change in score over the first 72 h of admission could be a standard of care, whilst accepting that this may need to be reviewed based on other institutions' findings.

Keywords: intensive care, audit

Reference

1 Le Gall JR, Klar J, Lemeshow S, *et al JAMA* 1996, **276**. 802–10

The protective effect of hydroxyethyl starch on pulmonary function in infra-renal aortic surgery is independent of neutrophil elastase

D. Rittoo[1], P Gosling[2], S Burnley[3], C Bonnici[3], P Millns[3], M. H Simms[1], S R G Smith[1] and R K. Vohra[1]

[1]*Department of Vascular Surgery,* [2]*Department of Biochemistry, and* [3]*Department of Anaesthetics and Intensive care, Selly Oak Hospital, Raddlebarn Road, Birmingham B29 6JD, UK*

Background: Previous investigations have suggested that neutrophil derived proteinases play a significant role in the development of ischaemia–reperfusion (I–R) related lung injury. Hydroxyethyl starch solution has been shown to protect against the I–R induced injury in animal models.[1]
Aims: To investigate the effects of volume expansion with hydroxyethyl starch (eloHAES) on pulmonary function and neutrophil elastase release (NER).
Patients and methods: Twenty patients undergoing infra-renal elective aneurysm surgery were randomly allocated to receive either gelofusine or eloHAES solution. Urinary albumin excretion and plasma elastase were measured pre-operatively (T0), before cross clamp of the aorta (T1), after reperfusion (T2), subsequently four hourly for 12 h (T3,4,5), and on the first postoperative day (T6). The albumin excretion was expressed as albumin creatinine ratio (ACR) in mg mmol^{-1}, and the plasma elastase in µg litre^{-1}

Table 31 Albumin creatinine ratio (ACR), plasma elastane (NER) and lung injury score (LIS) following eloHAES or gelofusine during elective aortic aneurysm repair. * $P<0.05$, ** $P = 0.03$ Mann–Whitney test

		T0	T1	T2	T3	T4	T5	T6
ACR	eloHAES	2.70	7.00	6.95*	4.75*	2.95	2.20	2.80
	gelofusine	2.35	14.05	16.3	8.4	2.55	2.1	2.4
NER	eloHAES	–	47	108	106	104.5	98	102
	gelofusine	–	73	107	99	100	114	127
LIS	eloHAES	0	0	0**	0**	0**	0.5	0
	gelofusine	0	0	1	1	1	0.5	1

These were correlated with the lung injury score (LIS) determined by Pa_{O_2}/F_{IO_2}, chest X-ray and lung compliance.

Results: The ACR increased in all patients following reperfusion and was lower in the eloHaes group indicative of less systemic capillary leaks (Table 31). The LIS was significantly lower in the eloHAES treated patients for up to 8 h following reperfusion. There was no difference in neutrophil elastase during the study period.

Conclusions: EloHAES reduces systemic protein extravasation and limits pulmonary dysfunction. This effect appears to be independent of elastase release.

Keywords: lung, function; enzymes, elastase

Reference

1 Oz MC, Zikria BA, McLeod PF *et al. Surg Forum* 1989, **40**: 48–50

Effect of inspiratory waveform on pulmonary ventilation and gas exchange

M. Ravishankar[1] and **M. Naushad**[2]

[1]Department of Anaesthetics and Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) Hospital, Pondicherry, India [2]Noble's Hospital, Douglas, Isle of Man IM1 4QA, UK

The effect of square (constant) and decelerating inspiratory waveform on pulmonary ventilation and gas exchange were studied on 20 patients with apparently normal lungs, who were mechanically ventilated in volume controlled mode using Puritan Bennett 7200 respirator. The conventional ventilatory parameters like the tidal volume, respiratory rate, positive end expiratory pressure (PEEP), inspiratory to expiratory ratio (I/E ratio), inspiratory pause duration and inspired oxygen concentration (F_{IO_2}) were all kept constant throughout the 4-h study period. The square waveform was applied for the initial 2 h followed by decelerating waveform for the next 2 h.

The parameters monitored every hour, for 4 h included peak, mean and plateau pressures; respiratory mechanics as resistance and static compliance. The arterial blood gases were sampled to measure the oxygen tension (Pa_{O_2}), carbon dioxide tension (Pa_{CO_2}), the hydrogen ion concentration (pH), the alveolar – arterial oxygen gradient A-a(DO_2), the arterial – alveolar oxygen ratio (a/A ratio) and the shunt fraction (Qs/Qt) with the help of Slide rule assessment[1] of venous admixture; haemodynamics like heart rate, non-invasive blood pressure, central venous pressure, arterial oxygen saturation, temperature and urine output.

Statistical analysis was performed using one way ANOVA with $F<0.05$ as significant followed by Student's '*t*' test for paired samples with P value <0.005 as significant.

Decelerating flow pattern produced significant reduction of peak airway pressure and shunt fraction (Table 32).[2] A significant improvement in oxygenation with increase in mean airway pressure[2] and resistance was observed. There was near significant increase in the compliance[2] and no significant change in the alveolar–arterial oxygen gradient, arterial carbon dioxide tension, acid–base status and haemodynamics when compared to the square flow pattern.

Table 32 Effect of inspiratory waveform on ventilation and gas exchange parameters (mean (SD)). $f<0.05$, $P<0$ 005

	Peak flow	Peak press	Mean press	Resist	Pa_{O_2}	a/A	Qs/Qt
Square wave	30 50 (5 1)	22 90 (3 5)	9 097 (0 95)	8.955 (2 1)	134.38 (20 4)	0 645 (0.10)	6.16 (2 4)
Decel wave	55 05 (8 2)	20 02 (2.9)	9.69 (0.92)	11 24 (2 1)	145.13 (22.1)	0 699 (0.11)	5 05 (2.4)
F value	0.0000	0 0002	0 0056	0.0000	0.0268	0 0277	0 0460
P value	0 000	0 000	0 000	0 000	0.000	0.000	0 000

Keyword: ventilation

References

1 Zetterstorm H. *Acta Anaesthesiol Scand* 1989; **33**: 250–4
2 Al-Saady N, Bennett ED. *Intensive Care Med* 1985, **11**: 68–75

The anaesthetic aspects of performing percutaneous tracheostomies in intensive care: report of a postal survey

C. Patel[1] and A. C. Beaumont[2]

[2]Intensive Care Unit, East Kent Hospital, Ethelbert Road, Canterbury CT1 3NG, UK. [1]Anaesthetic Department, King's College Hospital, Denmark Hill, Camberwell, London SE5 9RS, UK

There have been several reports in recent literature regarding various anaesthetic techniques used in performing percutaneous tracheostomies in the intensive care unit (ICU) [1] A postal survey was designed to assess the routine practice for this procedure on the Intensive Care Unit.

A 1-page, tick-box questionnaire was sent to the clinical directors of 237 ICUs in the United Kingdom. The questionnaire could be answered anonymously. The 12 main questions asked were: (1) Do you perform percutaneous tracheostomies on your ICU? (2) Do you take any patients to the operating theatre for percutaneous tracheostomies? (3) Do you routinely stop nasogastric feeding before the procedure? (4) Do you give the patient 100% oxygen? (5) Do you paralyse the patient? (6) Which anaesthetic technique do you routinely use? (7) Do you routinely use endoscopic guidance? (8) Who maintains the airway? (9) How is the airway maintained? (10) Do you routinely use capnograhy? (11) Do you leave the patient attached to the ICU ventilator or use an anaesthetic machine? (12) Have you encountered any problems with airway management during the procedure?

There were 185 replies, producing a response rate of 78%. Of those who responded, 159 (86%) routinely performed percutaneous tracheostomies on the ICU and 14 (7.6%) also occasionally performed percutaneous tracheostomies in theatre. Of the 159 ICU's that performed percutaneous tracheostomies, 148 (93%) aspirate the nasogastric tube immediately prior to the procedure. Of these, 141 (88.7%) also stopped nasogastric feeding at varying intervals in advance of the procedure. There were 155 (97.5%) units that administered 100% oxygen during the procedure, and 144 (90.6%) units paralysed the patient. Of the varying anaesthetic techniques used, 80 (50.3%) used a combination of intravenous sedation and local infiltration, 71 (44.7%) used intravenous sedation alone and 5 (3%) used an inhalational technique with or without local infiltration and/or intravenous sedation. Eighty-seven (54.7%) units routinely used endoscopic guidance as part of the procedure and in 53 (61%) of these units the same person who performed the endoscopy also maintained the airway. In nearly all units, 158 (99.3%), the airway was maintained by an intensivist or an anaesthetist, who in 129 (81%) units pulled back the standard endotracheal tube. The other methods employed for airway maintenance included the insertion of a micro-laryngeal tube, laryngeal mask airway or a high-pressure low volume tube. Only 50 (31.5%) used capnography. In most units, 151 (95%), the patient was left attached to the ICU ventilator and 6 (4%) used an anaesthetic machine as the method of ventilation. The most common complications encountered were puncture of the cuff, endotracheal tube or the posterior tracheal wall. Loss of airway and minor bleeding were also frequently reported.

Keyword: intensive care

Reference

1 Moe KS, Stoeckli SJ, Schmid S, Weymuller EA Jr. *Ann Otol Rhinol Laryngol* 1999; **108**: 384–91

Safety of interhospital transport of critically ill patients: specialist and non-specialist transfer teams

M. Hughes[1], G. Hilditch[1], F N. MacKirdy[2], J. Harten[1] and L. Plenderleith[1]

[1]*Clinical Shock Study Group, Intensive Care Unit, Western Infirmary, Dumbarton Road, Glasgow G11 6NT, UK.* [2]*Scottish Intensive Care Society Audit Group (SICSAG), Victoria Infirmary, Langside Road, Glasgow G42 9TY, UK*

In a drive to improve the standard of interhospital transport of critically ill patients, regional transport teams have been established. However, there is no evidence that such services improve mortality in intensive care units (ICU).

The SICSAG collate data collected on consecutive admissions to adult general ICU in Scotland. A preliminary investigation of its database was conducted to compare mortality after transport by a regional transport team with mortality after transport by non dedicated teams. Those patients transferred to participating ICU from 1/1/95 to 30/6/98 ($n = 1805$) were identified. A total of 106 patients were excluded from severity scoring. Patients transferred by The Clinical Shock Study Group, a specialised regional transport team, were identified using the team's database.

The regional transport team transferred 583 patients. The median Acute Physiology And Chronic Health Evaluation (APACHE) II score for the first 24 h of admission to ICU was 19. The Standardized Mortality Ratio (SMR) was 0 92 with 95% confidence intervals (CI) of 0.83–1.02. Those patients not transferred by the specialist transfer team numbered 1102 and had a median APACHE II score of 17. The SMR was 0.94 with CI of 0.86–1.02.

These figures provide no evidence that patients transferred by specialized regional transport teams have a lower mortality than those not transferred by a dedicated team.

It is clear that transport is only one of the many variables that influence mortality. The differences may simply not be measurable. In addition, the timing of APACHE II scoring in transferred patients is notoriously difficult. Therefore calculated SMR may be erroneous, though both groups should be affected by the same variables in this calculation. Lastly, in recent years authoritative guidelines have suggested that transfers be undertaken by competent experienced staff of an appropriate speciality.[1] This has been reflected by some gradual improvements in the quality of interhospital transfers.[2]

Keywords: intensive care, transfer

References

1 The Intensive Care society. Guidelines for the transfer of the critically ill adult. The Intensive Care Society, 1997

2 Knowles PR, Bryden DC, Kishen R, Gwinnutt CC. *Anaesthesia* 1999, 54: 283–9

Demographics of critically ill transferred patients

G. Hilditch[1], M. Hughes[1], F. N. MacKirdy[2], I. Lang[1] and L Plenderleith[1]

[1]*Clinical Shock Study Group, Intensive Care Unit, Western Infirmary, Dumbarton Road, Glasgow G11 6NT, UK.* [2]*Scottish Intensive Care Society Audit Group (SICSAG), Victoria Infirmary, Langside Road, Glasgow G42 9TY, UK*

There are few reports describing the demographic details and outcome of critically ill patients transferred into intensive care units (ICU) from other hospitals. We analysed the SICSAG database containing data which are collected on consecutive admissions to adult general ICU in Scotland.

Between January 1, 1995 and December 31, 1997 there were a total of 20 738 ICU admissions, of which 1805 (8.7%) were admitted after transfer. A total of 106 patients were excluded from the severity scoring. Transferred patients had a median age of 55 yr with a range of 16–89 yr. The mean Acute Physiology And Chronic Health Evaluation (APACHE) II score for the first 24 h of ICU admission was 18.3 and the Standardized Mortality Ratio (SMR) was 0.94 with 95% confidence intervals (CI) of 0.88–1.0. For hospital survivors the mean APACHE II score was 16. A total of 509 (30%) patients died in hospital and in this group the mean APACHE II score was 23.7. The median length of stay (LOS) in ICU was 4.2 days, and an interquartile range (IQR) of 1.55–10.0 days in all patients. In survivors the median LOS in ICU was 4.6 days, with an IQR of 1.7–10.2 days, compared with a median LOS of 3.1 days (IQR of 1 1–9.6) in ICU non-survivors.

There were 105 different diagnostic categories for transferred patients. These have been further classified into: respiratory 24.5%, cardiovascular 21.2%; trauma 14.8%; gastrointestinal 12.1%; neurological 9 7%; other 6 4%; sepsis 5.5%; renal 3.6%, hepatic 1.4% and haematological 0.7%

It is surprising that only 3.6% of transferred patients had a primary renal disorder. This may reflect that the increasing use of haemofiltration in ICU has led to a reduction in tertiary referral in these patients. This preliminary analysis also demonstrates that 45.7% had a primary respiratory or cardiovascular diagnosis, compared to 28% reported previously.[1] However, the reason for admission to ICU is not necessarily the same as the reason for transfer.

Further work is required to identify relevant differences in demographics and outcome between this group and patients who have not been transferred.

Keywords: intensive care; transfer

Reference

1 Reeve WG, Runcie CJ, Reidy J, Wallace PGM. Current practice in transferring critically ill patients among hospitals in the west of Scotland. *BMJ* 1990; **300**: 85–7

Safety of interhospital transport of critically ill patients

M. Hughes[1], G. Hilditch[1], F. N MacKirdy[2], I. Lang[1] and L. Plenderleith[1]

[1]*Clinical Shock Study Group, Intensive Care Unit, Western Infirmary, Dumbarton Road, Glasgow G11 6NT, UK.* [2]*Scottish Intensive Care Society Audit Group (SICSAG), Victoria Infirmary, Langside Road, Glasgow G42 9TY, UK*

Transport of critically ill patients has been associated with significant haemodynamic complications.[1] However, it has also been shown that it can be accomplished safely.[2] Therefore we sought to ascertain whether interhospital transport of critically ill patients, undertaken by a specialist regional transport team, influences mortality.

The SICSAG collate data collected on consecutive admissions to adult general intensive care units (ICU) in Scotland and identified 20 738 ICU admissions to 23 units between January 1, 1995 and December 31, 1997. The database of a regional specialist transport team allowed us to identify those patients transferred by the team to ICU for both bedspace problems (n = 307) and for upgraded facilities (n = 276).

The mean Acute Physiology And Chronic Health Evaluation (APACHE) II score in the Scottish population was 18.3, and the Standardized Mortality Ratio (SMR) was 0.95 with 95% confidence intervals (CI) of 0.93–0.97 Patients transferred by the regional transfer team had a mean APACHE II score for the first 24 h of ICU admission of 19 and the SMR was 0.93 (CI = 0.86–1.00). In those transferred for bedspace shortage, the mean APACHE II score was 18 and the SMR was 0.81 (CI = 0.67–0.94). For patients transferred requiring upgraded facilities the mean APACHE II score was 20.7 and the SMR was 1.06 (CI of 0.93–1.18).

This preliminary analysis demonstrates no significant difference in SMR between transferred patients and ICU patients Transport by a regional transfer team, therefore, appears not to improve mortality.

In comparison with the overall SMR for transferred patients, there are trends for lower SMR for bedspace transfers and higher SMR for upgrades. Although these do not reach statistical significance, they presumably reflect the different case mix of the two groups.

Keywords· intensive care; transfer

References

1 Braman SS, Dunn SM, Amico CA, Millman RP. *Ann Intern Med* 1987; **107**: 469–73

2 Ehrenwerth J, Sorbo S, Hackel A. *Crit Care Med* 1986; **14**: 543–7

What stress ulcer prophylaxis do you use?

R. Carr and **J. Casement**

Intensive Care Unit, City General Hospital, Stoke-on-Trent, Staffordshire ST4 6QG, UK

The subject of stress ulcer prophylaxis has been an area of controversy in critical care medicine, both as to whom should receive prophylaxis and with what agent. Recent evidence has clarified those patients most at risk (respiratory failure and coagulopathy)[1] and shown the superiority of H_2 antagonists[2] at preventing upper gastrointestinal haemorrhage without a significant increase in nosocomial pneumonia. A recent editorial[3] has suggested that we not only look at what and when we use prophylaxis, but also its cost effectiveness. We have assessed the current clinical practice in the 24 ITUs within the West Midlands Region.

A point prevalence telephone questionnaire of stress ulcer prophylaxis was carried out. The questions were directed to the senior nursing or medical staff. These were:

(1) Does your unit have a stress ulcer prophylaxis protocol?
(2) If yes, is prophylaxis routine, or do you target high-risk groups?
(3) If no is it left to the individual clinician to make a decision regarding prophylaxis?
(4) What prophylaxis is used?
(5) How many patients are on your unit today?
(6) How many are receiving prophylaxis and what type?

Table 33 Protocols for stress ulcer prophylaxis

Drug used	Protocol used, routine prophylaxis	Protocol used, targeted prophylaxis	No protocol used	Total
Sucralfate	0	0	2	2
Ranitidine	4	3	15	22

A total of 112 patients were in ITU beds on the day of the study Fifty-six were receiving prophylaxis, 51 of these were on ranitidine and five were on sucralfate. Two patients were receiving proton pump inhibitors for active gastrointestinal bleeding.

The majority of units had no protocol for the use of stress ulcer prophylaxis. All units with, and most units without, a protocol used ranitidine (Table 33). The use of sucralfate was confined to only two units, which did not have a protocol. Few of the protocol units however targeted their usage of prophylaxis at the high-risk patient. In units without a protocol we were unable to assess whether there was targeted or routine prophylaxis. The majority of units in our region follow best available evidence as regards the type of agent for prophylaxis. Use of ranitidine is more prevalent than in a previous study, 91% *vs* 46% of units surveyed.[4] Units which continue to give 'blanket' prophylaxis rather than restrict its use to those at high risk reduce the cost effectiveness of prophylaxis.

Keywords: intensive care; complications, ulcers

References

1 Cook D, Fuller H, Guyatt G, *et al. N Engl J Med* 1994; **330**: 377–9

2 Cook D, Guyatt G, Marshall J, *et al. N Engl J Med* 1998; **338**: 791–7

3 Tryba M *Crit Care Med* 1999; **27**: 16–17

4 Wyncoll DLA, Roberts PC, Beale RJ, McLuckie A. *BMJ* 1997; **314**: 1013

Are we any better at predicting pulmonary artery occlusion pressure?

D. Cameron, K. Brown, I Grant, N Leary, M. Fried and A Lee

Department of Anaesthetics, Intensive Care Unit, Royal Infirmary of Edinburgh, Edinburgh EH3 9YW, UK

The usefulness of pulmonary artery catheterization in the critically ill is questionable,[1] but the measurement of haemodynamic variables permits a rational approach to management The placement of pulmonary artery flotation catheters (PAFCs) is influenced by the perceived inability of the clinician to determine haemodynamic status from clinical evaluation alone.[2] After 20 yr of experience in the use of the pulmonary artery catheter are we any better at predicting what we are measuring?

Four intensive care units in the South East of Scotland participated over a 6-month period. Pulmonary artery occlusion pressure (PAOP) and cardiac index were estimated immediately before PAFC placement. This abstract is confined to the results of PAOP estimations and actual values. In advance of analysis a difference of ±3 mmHg was considered clinically insignificant. Actual values were divided into three bands: <8 mmHg, 8–16 mmHg and >16 mmHg

Data on 92 patients were suitable for analysis. Four patients were excluded due to incomplete information. The mean age was 61 yr. The PAFC was placed within 48 h of admission to the Intensive Care Unit in 87 patients. In 70 patients the placement of the PAFC was consultant directed. Sixty-one patients (66.3%) had a clinically insignificant difference between predicted and actual PAOP Of the remaining 31 patients (33.6%), 11 patients were just out with the set criteria (4 mmHg difference) and this did not affect their management. Thirteen patients had estimations and actual measurements which were in different bands. Actual PAOP measurement revealed nine of these patients to be underfilled (six septic, three others). Two septic patients, estimated to be very underfilled, had elevated actual PAOP measurements (predicted PAOP 5 and 12 mmHg, actual PAOP 25 and 20 mmHg respectively). Prediction of pulmonary artery occlusion pressure is generally accurate, however clinical judgement may fail to diagnose significant underfilling in patients with sepsis. It is debatable whether PAOP accurately reflects volume status, but five of these patients had a measured PAOP of 4 mmHg or less, and only one of these patients was judged to be underfilled Two patients who were shocked (meningococcal septicaemia and bowel obstruction) were judged to be underfilled, but both had a PAOP ≥20 mmHg. It is hard to believe that this did not represent undiagnosed myocardial dysfunction.

PAFC placement remains a useful diagnostic and management tool in a small number of shocked septic patients.

Keywords: arterial pressure; equipment, catheters, arterial

References

1 Connors AF *et al. JAMA* 1996, **276** 889–97
2 Connors AF, McCaffree DR, Gray BA. *N Engl J Med* 1983, **308**· 263–67

Impact of a standard insulin sliding scale on the efficacy of controlling blood glucose levels in the critically ill

G. O'Callaghan and R J Beale

Department of Adult Intensive Care, Guy's and St Thomas Hospitals, Lambeth Palace Road, London SE1 7EH, UK

We tested the hypothesis that a standard insulin sliding scale as a starting point for insulin therapy in the critically ill would improve control of blood glucose levels as evidenced by decreased times to achieve a blood glucose level (BGL) of less than 10 mmol litre^{-1} from the commencement of intravenous insulin. The current practice guidelines dictate that BGL's should initially be done hourly when abnormal and insulin therapy started if the BGL is greater than 10 mmol litre^{-1} for 3 h. We audited the efficacy of these guidelines over a 4-week period and repeated this process following introduction of a standard insulin sliding scale (Table 34) as a starting point for insulin therapy.

There were 15 patients who required insulin infusions in the first 4-week period. The mean time taken to initiate therapy following the third abnormal BGL was 3.3 h and to achieve a BGL of <10 mmol litre^{-1} was 8.2 h, the mean time taken between the first and third abnormal BGL was 6.9 h. Following introduction of the standard sliding scale there were nine patients who required insulin infusions during the period of audit. The time taken to initiate therapy was reduced to 0.4 h ($P = 0.09$) while the time taken to achieve a BGL of <10 mmol litre^{-1} was reduced to 6 h ($P = 0.32$). The time between the first and third BGL which provides a useful index of compliance with practice guidelines was reduced to 3 h ($P = 0.23$).

The use of a standard sliding scale seems to facilitate more expedient control of blood glucose levels and its introduction increased compliance with established practice guidelines The small sample size does not achieve statistical significance.

Keywords· metabolism, insulin

Table 34 Standard insulin sliding scale *BGL should be done hourly until infusion rates are lower. Make sure if feeding is stopped infusion rates are adjusted accordingly

Blood glucose level mmol litre^{-1}	Actrapid infusion iu i.v. h^{-1}
0–5.9	0
6–7.9	0.5
8–9.9	1
10–11.9	2
12–13.9	4
14–15.9	6*
16–17.9	8*
18–20	10*
20	15*

In vitro validation of the Tonocap® and a modified Paratrend 7® sensor

R. Hurley, M. Grocott and M G Mythen

Centre for Anaesthesia, The Middlesex Hospital, Mortimer Street, London W1N 8AA, UK

Introduction: The assessment of splanchnic perfusion by measuring gastric luminal $P\text{CO}_2$ is a clinically useful technique. The Tonocap® (Datex-Ohmeda) has been validated for such use but only provides a reading every 10 min. The Paratrend 7® Sensor (Diametrics Medical Ltd) is a device used for continuous blood gas monitoring capable of responding to changes in $P\text{CO}_2$ within 15 s. Recently, sublingual measurement of $P\text{CO}_2$ has been described as a new method of assessing splanchnic perfusion.[1] We modified the Paratrend 7® sensor by encasing it in a plastic sleeve in order to protect it as would be necessary for sublingual use. It was then compared with the Tonocap® by placing them both in a water bath.

Methods: A vigorously stirred water bath of saline at a constant temperature of 37°C was bubbled with standard calibration gas mixtures of 5% and 10% CO_2 with predicted CO_2 tensions being calculated from atmospheric pressure and corrected for water saturation of the bath A Trip® catheter (Tonometrics) connected to a Tonocap® was placed in the water bath alongside two Paratrend 7® sensors, one covered by a plastic sheath, the other unsheathed. The sheath consisted of the plastic tubing from a Butterfly®-19 (Venisystems-) which had a 2 cm eye cut at the end to allow more contact with the sensor but provided protection The Tonocap® was left to equilibrate in the water bath for 30 min. A total of 52 paired readings were taken at 10-min intervals

Results: Table 35 shows the bias and precision of each measurement technique as a percentage of predicted values

Conclusions. The results for the Tonocap® and Paratrend 7® (unsheathed) are similar to previously reported studies.[2] The sheathed Paratrend 7® was also shown to give a very accurate reading of $P\text{CO}_2$ with a very small negative bias and excellent precision

Keywords: equipment, analysers, carbon dioxide

Table 35 Bias and precision of each measurement technique as a percentage of predicted values

	Tonocap		Paratrend (unsheathed)		Paratrend (sheathed)	
CO_2	Bias	Precision	Bias	Precision	Bias	Precision
5%	–3.17%	2.1%	–1.49%	0.5%	–2.62%	0.44%
10%	–1.41%	1.8%	–0.47%	0.84%	–1.84%	0.91%

Acknowledgement

This study was supported by Datex-Ohmeda, Diametrics Medical Ltd and The Centre for Anaesthesia

References

1 Nakagawa Y, Weil MH, Tang W, *et al* *Am J Respir Crit Care Med* 1998; **157:** 1838–43

2 Venkatesh B, Morgan J, Jones RDM, Clague A *Anaesth Intensive Care* 1998, **26:** 46–50

Assessment of neuromuscular function in intensive care patients and volunteers

I. McGovern[1], A. Cunliffe[2] and D R Goldhill[1]

[1]Anaesthetics Unit, The Royal London Hospital, London E1 1BB, UK.
[2]Department of Biomedical Sciences, University of Westminster, London W1M 8JS, UK

Neuromuscular abnormalities are well recognized in long-term critically ill patients.[1] While the study of involuntary skeletal muscle function has been extensive in the field of nutrition assessment, attempts to apply these techniques in the ICU setting have been plagued with technical difficulties.[2]

The contraction and relaxation characteristics of the adductor pollicis muscle of the thumb following transcutaneous ulnar nerve stimulation were studied in (34) volunteers and (17) patients admitted to the ICU. Patients were excluded if they were receiving neuromuscular blocking drugs or were known to be paralysed as a result of previous illness or current injury.

The ratio of force generated by supramaximal stimulation at 10 Hz to that at 30 Hz (F10/30), the maximal relaxation rate of the muscle following stimulation at 30 Hz (MRR30) and the duration of stay in ICU (days) at the time of testing were measured. Statistical analysis of the differences between the ICU groups and the volunteers used the unpaired Student *t* test or the Mann–Whitney U test where the data was non-normally distributed.

From an attempted 31 measurements in the ICU group 28 acceptable traces were obtained (Table 36); lack of patient co-operation being the main impediment. Although the majority of volunteers and conscious ICU patients perceived nerve stimulation as uncomfortable, none described the sensation as unacceptable and no long-term morbidity was associated with the technique. A significantly higher mean F10/30 and a lower mean MRR30 were measured in the ICU group compared with volunteers. Differences were greater when those patients tested after having spent more than 7 days on the ICU were analysed separately.

Despite some limitations in the applicability of this technique for assessment of all ICU patients it has the potential to provide a non-invasive method of quantifying and monitoring the progression of neuromuscular dysfunction in this setting.

Keywords: neuromuscular function; intensive care; complications, neuromuscular disorders

Table 36 Neuromuscular function in ICU patients and normal volunteers
Values are means (SEM). Asterisks signify significant difference from volunteers (*P<0.05, **P<0.01, ***P<0.001)

	F10/30 (%)	MRR30 (% maximal force loss 10 ms^{-1})
Volunteers (n = 34)	35.15 (1.53)	11.25 (0.36)
ICU ≤7 days (n = 19)	42.42 (4.25)	8.44 (1.07)**
ICU >7 days (n = 9)	50.89 (6.46)*	7.23 (0.61)***
All ICU traces (n = 28)	45.14 (3.57)**	8.05 (0.75)***

References

1 Coakley JH, Nagendran K, Honavar M, *et al.* *Intensive Care Med* 1993, **19:** 323–8

2 Finn PJ. Plank LD, Clark MA, *et al* *J Parenter Enteral Nutr* 1996; **20:** 332–7

Pre-treatment with high density lipoprotein (HDL) attenuates the renal and hepatic dysfunction caused by endotoxin in rats

P. Dhadly, M. C. McDonald, G. Cockerill[1], C. J. Hinds[2], N. E. Miller[1] and C Thiemermann

The William Harvey Research Institute, [1]Department of Cardiovascular Biochemistry and [2]Department of Intensive Care, St Bartholomew's and The Royal London School of Medicine and Dentistry, Charterhouse Square, London EC1 6BQ, UK

Introduction: High-density lipoprotein (HDL) binds to lipopolysaccharide[1] (LPS), has anti-inflammatory properties[2] and exerts beneficial effects in some, but not all, models of endotoxaemia.[3] Here we investigate the effects of HDL on the multiple organ injury and dysfunction caused by endotoxin in the rat.

Methods: Male Wistar rats (n = 33) were anaesthetized with sodium thiopental (120 mg kg^{-1} i.p) and instrumented for the measurement of blood pressure. At 30 min after surgery, animals were pre-treated with HDL (80 mg kg^{-1} i.v , n = 9) or with saline (4 ml kg^{-1} iv, n = 10) and 5 min later they received *E. coli* LPS (6 mg kg^{-1} i.v) as a slow injection over 20 min. In addition, two groups of rats which had received vehicle rather than LPS (sham-operated animals) were also pre-treated with either HDL (n = 4) or saline (n = 6). All rats received an infusion of saline (1.5 ml kg^{-1} h^{-1})

Results: Four out of 14 rats treated with saline and 0 out of 9 rats treated with HDL died within 6 h of administration of LPS and were excluded from further analysis. Endotoxaemia caused a bi-phasic fall in blood pressure as well as liver and pancreatic injury (determined by serum levels of AST, ALT and lipase) and renal dysfunction (increase in serum levels of urea and creatinine). Pre-treatment of rats with HDL significantly attenuated the renal and hepatic injury (P<0.05; ANOVA followed by Dunnett's test for multiple comparisons), but exacerbated the acute hypotension caused by LPS. In rats which had not received endotoxin, HDL had no effect on blood pressure or organ dysfunction.

Conclusion: Pretreatment with HDL attenuates the renal and hepatic injury/dysfunction associated with severe endotoxin shock in the rat. The mechanism of this beneficial effect of HDL warrants further investigation.

Keywords: rat; endotoxin

References

1 Ulevitch RJ, Johnston AR, Weinstein DB. *J Clin Invest* 1979, **64:**1516–24

2 Pajkrt D, Doran J, Koster F, Lerch P, *et al.* *J Exp Med* 1996; **184:** 16018

3 Levine D, Parker T, Donnelly T, Walsh A, *et al.* *Proc Natl Acad Sci USA* 1993; **90:** 12040–4

Early detection of the covert onset and evolution of critical illness polyneuromyopathy

D. D. Kennedy, S. N Fletcher, I. R. Ghosh, C. J. Hinds and J H Coakley

Intensive Care Units, St Bartholomews Hospital, West Smithfield, London EC1A 7BE, and Homerton Hospital, London E9 6SR, UK

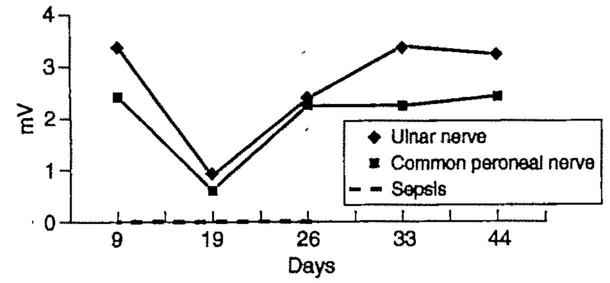

Fig 3 Change in CMAPs in a representative patient.

Introduction: Critical illness polyneuropathy was first identified by Bolton and colleagues[1] and weakness due to neuropathic and/or myopathic abnormalities is now recognized as a common complication of prolonged critical illness.[2] The presence of abnormally low compound motor action potentials (CMAPs) is considered an important diagnostic criterion. The onset and evolution of this condition following intensive care unit admission has not previously been systematically investigated.

Methods: A prospective, sequential study of all patients thought likely to require intensive care for 7 days or more was performed over a 12-month period. Admission APACHE II score, daily organ failure score, presence of sepsis, ventilation mode and routine haematology and biochemistry results were recorded. A daily neurological examination and weekly neurophysiological studies were performed for the duration of the patients' ICU stay. The neurophysiological studies included CMAPs, nerve conduction velocities, sensory action potential amplitudes and electromyography. The Spearman correlation coefficient was used to analyse associations between the recorded physiological data and serial CMAPs. In our institution the lower limits of normal for ulnar and common peroneal nerve CMAPs are 2.5 and 2.8 mV respectively.

Results: Thirty-two patients were recruited to the study, of whom 23 survived for 7 days or longer. One patient was withdrawn at a relative's request and two patients continued to receive muscle relaxants until death. The median age was 61 yr (range 33–80) and median admission APACHE II score was 20 (9–33). A significant positive correlation was found between serum albumin and CMAPs ($P<0.05$). CMAPs of one patient are shown in Fig 3. Thirteen patients had three or more sets of neurophysiological studies. CMAPs were found to be low or fell during episodes of sepsis, at a time when it was not possible to detect weakness clinically, and CMAPs recovered as sepsis subsided. Of the eight patients who survived, six had severe clinical weakness of MRC grade 3 or less.

Conclusions: The onset of critical illness motor syndrome may precede by days or weeks clinically detectable weakness, seems to be associated with episodes of sepsis and can occur within days of the onset of sepsis. Recovery in CMAPs may be equally rapid as sepsis subsides.

Keywords: complications, neurological

References

1 Bolton CF, Gilbert JJ, Hahn AF, Sibbald WJ. *J Neurol, Neurosurg Psychiatr* 1984; **47**: 1223–31
2 Coakley JH, Nagendran K, Honavar M, Hinds CJ. *Intensive Care Med* 1993; **19**: 323–8

Tracheostomy: the change in practice in a region over a decade

M. K. Street, O. Boyd on behalf of South Thames Intensive Care Committees

Table 37 Complications and technique of tracheostomy

	Ciaglia	Portex	Surgical	Missing/combined
Numbers	138	93	23	7
Complications	29%	38%	52%	

Royal Sussex County Hospital, Eastern Rd, Brighton, East Sussex BN2 5BE, UK

Since the introduction of pecutaneous tracheostomy by Ciagla in 1985 practice has inevitably changed.[1] Two common minimally invasive techniques are in widespread usage. The Ciaglia method uses a wire guided dilational technique with increasing size plastic dilators to produce a tract for the insertion of the tracheostomy tube. The Portex technique which after location of the trachea with a needle and wire uses instrumental dilatation to assist the insertion of the tracheostomy tube.

A prospective survey was conducted in the South Thames Region over a 6-month period from November 1997 to May 1998. Details of the type of technique, peri-insertion complications, seniority of the operator and supervisor together with the use of brochoscopic assisted placement were recorded.

Twenty-two intensive care units, 62% of the total, contributed data on 261 ventilated patients undergoing tracheostomy (Table 37).

No mortality associated with the techniques was recorded and the incidence of severe complications was 3.4%. Over all the incidence of minor complications was 25%, the most common being bleeding. Estimated blood loss in excess of 25 ml was statistically higher in the surgical group when compared to the Ciaglia technique ($P = 0.000015$) or the Portex technique ($P = 0.019$). The incidence of bleeding was also higher in the Portex group when compared to the Ciaglia technique ($P = 0.012$).

The incidence of all complications appeared to unrelated to demographic factors, grade of operator supervision or the use of bronchoscopic assisted placement. No attempt was made to assess long-term complications, which have been the subject of several other previous studies.

The introduction of the new technique of pecutaneous tracheostomy seems to have gained wide spread adoption throughout the intensive care units of the south east of England. Despite the relative inexperience of those performing these procedures on long term ventilated patients the incident of clinically significant complications appears low.

Keywords: equipment, tracheostomy

Acknowledgement

Funding for this study was obtained from South Thames Region

Reference

1 Ciaglia P, Firsching R, Syniec C. *Chest* 1985, **87**: 715–9

Requesting donation: the satisfaction of the next-of-kin of potential organ donors

J. Morton[1], M. Morley[2], G Blok[3], J van Dalen[3]
[1]Department of Clinical Psychology, University of Liverpool, Liverpool L69 3GB, UK [2]Department of Clinical and Health Psychology, Manchester Royal Infirmary, Manchester M13 9WL, UK. [3]Department of Educational Research and Educational Development, Skillslab, University of Maastricht, PO Box 616, 6200 MD Maastricht, The Netherlands

The rate of organ donation is slowing in the UK, increasing pressure on healthcare staff to speak with families about donation. Intensive care staff are not confident that they have the necessary communication skills. They fear they may increase families' distress[1] and are not clear of the most helpful way to approach families.[2] The need for suitable training has been recognized.[3]

There is a need to investigate the potential donor families' experiences to identify helpful practice when delivering bad news and requesting donation. Retrospective in-depth semi-structured interviews were carried out by a clinical psychologist with bereaved next-of-kin of potential organ donors (n = 29). Twenty Northwest Intensive Care Units were involved. Kin were sequentially identified and interviewed 6 months after their bereavement. The interview was organized in temporal order, from arrival to departure. Key questions focusing on satisfaction with care and communication were repeated. Next-of-kin recalled their experiences and reactions and rated their satisfaction (1 = very dissatisfied, 7 = very satisfied) with unit practices. Protocol one recorded the accounts, responses to prompts and spontaneous comments. Protocol two recorded the ratings of satisfaction with the questions.

Whether consenting or refusing to donate, all kin found the request acceptable. Staff's tension when making the request was evident to families. The majority of kin rated themselves satisfied with the meeting to discuss donation (mean 6.3, SD 1.3), and explanations given (mean 6.0, SD 1.4). There was a relationship between satisfaction and the request being made separately from the news of death ($P<0.025$), the request following brain-stem death tests ($P<0.013$), and the meeting having a clear structure ($P<0.002$). Distress at the request itself, was evoked when kin had not understood their relative had died. Kin who had understood considered the request was 'business to be conducted', 'something positive in the middle of a tragedy'.

The practices, which are generally considered helpful to families, were not uniformly represented across units. There was evidence of potential unhelpful practice. The results suggest that increased distress is not related to the donation per se, but to whether the families have accepted the fact of death. Study results support the recommendations for training for staff involved in breaking bad news and requesting donation.

Keywords: intensive care, organ donation requests

References

1 Siminoff L, Arnold RM, Caplan AL. *J Trauma Inj Inf Crit Care* 1995; **39:** 553–9
2 Wakeford RE, Stepney R. *Br J Surg* 1989 **76**: 435–9
3 Intensive Care Society. *Guidelines for Bereavement Care in Intensive Care Units.* 1998

Sterile bred rats for studies involving septic challenges have differing levels of endogenous immunity to endotoxin core

R. Stephens[1], M Rashid[1], R. Barclay[2], R. Studwell[3], M Singer[3], D. Brealey[3], M Mythen[1], C Hamilton-Davies[1]

[1]*Centre for Anaesthesia, UCL Hospitals, University College London, London, UK* [2]*Scottish Blood Transfusion Service, Edinburgh, UK.* [3]*Bloomsbury Institute of Intensive Care Medicine, 5 University Street, London WC1E 6JJ, UK*

Background: Low levels of natural endogenous antibody to endotoxin core (EndoCAb) have been related to poor outcome after surgery[1 2] and sepsis.[3] Rats are often used in animal models of sepsis, but baseline EndoCAb status, which varies greatly in humans, is rarely determined in these animals The aim of this study was to determine if any significant differences existed between laboratory rats in baseline endotoxin immunity.

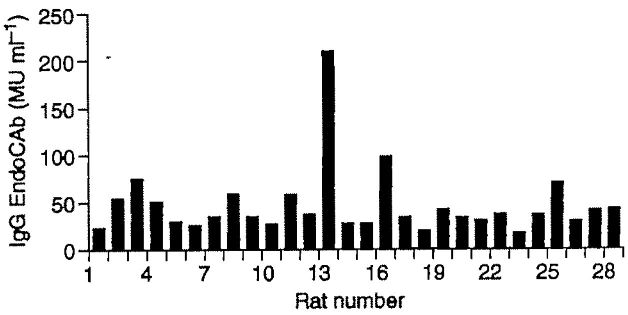

Fig 4 IgG EndoCAb levels in rats

Method: 35 sterile bred Wistar rats were anaesthetised with Isoflurane and blood 1 ml was removed by aseptic technique via cardiac puncture. This blood was then centrifuged at 2000 g for 10 min and serum separated. The serum was diluted 1:200 and 100 µl added to the ELISA wells which were pre-coated with a variety of core moieties of endotoxin. This was then incubated at 37°C for 1 h, washed and 1:500 alkaline phosphatase anti-rat IgG 100 µl added. After further incubation and washing, alkaline phosphatase substrate was added. This was left at room temperature until the colour developed to give a maximum optical density of approximately 2.0 at the top of the standard curve using an ELISA plate reader.

Results: These are shown in Figure 4.

Conclusions: This demonstrates that in animal experiments where there is supposed uniformity in a sterile bred population there remain vast differences in their underlying immunity to endotoxin which may affect the response to a septic challenge.

Keywords: rat; endotoxin

References

1 Bennet-Guererro E, Ayuso L, Hamilton-Davies C, *et al. JAMA* 1997; **277**: 646–50
2 Hamilton-Davies C, Barclay GR, Cardigan RA, *et al. Chest* 1997; **112:** 1189–96
3 Strutz F, Heller G, Kresemann K, *et al. Int Care Med* 1999; **25:** 435–44

Reduced fungal infection in critically ill patients randomized to a glutamine containing parenteral nutrition

K Allen[1], **R. D. Griffiths**[2] and C. Jones[2]
[1]*Microbiology Department, Whiston Hospital, Prescot L35 5DR, UK.*
[2]*Intensive Care Research Group, Department of Medicine, University of Liverpool, Liverpool L69 3GA, UK*

Candida infections are an important cause of nosocomial infection that increase with time in intensive care. This may be related to a progressive state of hypo-immunity. Glutamine (gln) is an important nutrient for the immune system and has been shown to enhance the helper T subset 1 (Th1) lymphocyte responses and cell-mediated immunity.[1] We report the incidence of bacterial and fungal infection that occurred during a randomized treatment study of glutamine supplemented parenteral nutrition (PN) versus a matched control parenteral feed in ventilated ICU patients unable to tolerate enteral feeding.[2]

Prospectively throughout the study the microbiologists attending the ICU collected microbiological data on all cultures obtained from ICU patients and any treatment decisions in laboratory

Table 38 Infection in patients receiving parenteral nutrition for more than 5 days, the effect of glutamine supplements

	Glutamine (n = 25)	Control (n = 27)
Age (median and quartile)	63 (44–71.5)	62 (50–72.5)
Days TPN (median and quartile	10 (7–13)	9 (6–16.5)
Died within 28 days of ICU	9	16
Total infective events	40	50
Candida infections (deaths)	4 (0)	9 (6)

notebooks. Data on those patients who received at least 5 days of parenteral nutrition were later extracted and analysed blind to the randomisation by one of the authors (KA). The frequency of infective incidents, types of organisms and types of infections was related to feed type and outcome at 28 days of discharge from ICU.

Fifty-two of the original 84 randomized patients received parenteral nutrition for more than 5 days. Sepsis was the most frequent diagnosis, with gastrointestinal disease accounting for 12/25 gln-PN and 10/27 control-PN respectively. Nine of 25 gln-patients and 16/27 control-patients died in ICU or within 28 days of discharge from ICU. In the first 5 days of TPN there were 14 gln *vs* 12 control infective events, compared with 23 gln *vs* 31 control infective events during the period after 5 days TPN, or post TPN period on ICU (3 gln *vs* 7 control). There was no difference in the total number of Gram-positive or Gram-negative organisms isolated. Only four patients in the glutamine group developed *Candida* infections and none died while nine control patients developed *Candida* infections and six died (P = 0.07, Fischer's exact test) (Table 38)

Any post hoc sub-group analysis must be interpreted with caution, especially with small numbers. However selecting a minimum of 5 days we believe is valid to show a nutritional effect. Immune dysfunction is a feature of a prolonged ICU stay and therefore any effect will only be shown in such patients. These clinical observations with a reduction in incidence and death among the patients with *Candida* infections suggest that glutamine may exert profound immune benefits in long stay critically ill patients who are dependent on parenteral nutrition.

Keywords: infection, fungal

References

1 Yaqoob P, Kew S, Wallace FA, *et al.* *Clin Nutr* 1998; **17**: 33
2 Griffiths RD, Jones C, Palmer TEA. *Nutrition* 1997; **13**: 295–302

Elimination of cytokines by the kidney: comparison between normal individuals and patients with severe sepsis or the systemic inflammatory response syndrome

C. M. H. Gómez[1], J. Sheldon[2], P. Riches[2] and M. G. A. Palazzo[1]

[1]Departments of Intensive Care, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK. [2]Immunopathology, St George's Hospital, Blackshaw Road, London SW17, UK

Cytokine elimination by the functioning kidney has received little attention. We have compared the filtration of pro- and anti-inflammatory cytokines between the normal kidney in healthy individuals and the functioning kidney in patients with severe sepsis or the systemic inflammatory response syndrome (SIRS).

We studied 32 individuals. Group I included 15 asymptomatic healthy volunteers from within the intensive care unit staff (six male, nine female; mean age 33.7 ± 6.4 yr, mean serum creatinine 40.3 ± 32.2 μmol litre^{-1}). All individuals had a serum creatinine below the upper limit of the normal reference range for our laboratory (105 μmol litre^{-1}) and no proteinuria. Group II included 17 patients with either severe sepsis or SIRS and normal or near normal kidney function (11 male, six female; mean age 56 ± 15; mean serum creatinine 116 ± 52 μmol litre^{-1}, mean plasma creatinine clearance 57 ± 34 ml min^{-1}, median APACHE II 20, median SAPS 37, median SOFA 8).

Group I individuals provided one sample of blood and urine. In group II patients eight matched blood and urine samples were taken at predefined intervals during a 24 h period on or close to admission. Blood was collected into lipopolysaccharide (LPS)-free tubes containing disodium ethylenediaminetetraacetic acid (EDTA). Urine was collected into sterile containers. After immediate centrifugation at 4°C at 4000 rpm the supernatants were stored at –70°C. Soluble tumour necrosis factor receptors (sTNFR) I and II, interleukin-6 (IL-6), TNFα and IL-10 were assayed by specific enzyme-linked immunosorbent assays (ELISA) (R&D Systems, Abingdon, Oxon, UK). For each cytokine and each subject we determined the following parameters: urine and plasma cytokine concentrations (U_c, P_c), urine to plasma cytokine ratio (U_c/P_c) and sieving coefficient (θ), defined as the urine to plasma cytokine ratio divided by the urine to plasma creatinine ratio. Group I individuals had one value determined for each parameter. Group II patients had the eight values determined for each parameter averaged to give a representative value for that parameter. Within group medians of each parameter were compared by the Mann–Whitney U test for non-parametric data. A P value of less than 0.05 was taken to represent statistical significance.

The urinary concentration of IL-6 in healthy volunteers was undetectable. The median sieving coefficients for group I were 0.0055, 0.006, 0.004 and 0.006 for sTNFRI, sTNFRII, TNFα and IL-10, respectively. For group II these were 0.255, 0.135, 0.035 and 0.053, respectively. In group II patients the median θ for IL-6 was 0.015. Compared with healthy subjects patients with SIRS/severe sepsis and functioning kidneys (group II) had a significantly higher urinary concentration, urine to plasma ratio and sieving coefficient (q) of sTNFR I, sTNFRII, TNFα and IL-10 (P<0.02).

In SIRS or severe sepsis the functioning kidney eliminates more pro-inflammatory as well as anti-inflammatory cytokines than the normal kidney of healthy individuals.

Keywords· kidney, function

ACE gene polymorphism is not associated with outcome in patients requiring admission to liver ITU with paracetamol-induced acute liver failure

N. Jackson, P Donaldson and J. Wendon

Institute of Liver Studies, Kings College Hospital, Denmark Hill, London SE5 8RX, UK

Introduction: Patients with paracetamol-induced acute liver failure have a clinical state resembling septic shock with progressive loss of vascular tone and endothelial dysfunction. Increased levels of NO in conjunction with pro-inflammatory cytokines are present in acute liver failure with a high incidence of multiorgan failure. The outcome, however, is unpredictable and is unrelated either to the quantity of paracetamol ingested or the severity of liver injury

There is a functional insertion (I)/deletion (D) variation in intron 16 of the ACE gene resulting in three genotypes II, ID and DD. The D allele is associated both with higher tissue ACE activity and with blunting of endothelial-dependant vasodilatation in response to NO. We investigated whether the ACE gene polymorphism might be associated the incidence and outcome of multiorgan failure in patients with paracetamol-induced acute liver failure

Patients and methods. 118 patients with severe paracetamol-

Table 39 ACE gene polymorphisms and outcome in acute liver failure patients ARF, acute renal failure, ARDS, acute respiratory distress syndrome

Patients (number)	**II**	**DI**	**DD**
All patients (118)	27%	50%	23%
Survivors (65)	32%	41%	26%
Non-survivors/transplanted (53)	21%	60%	19%
ARDS (25)	16%	60%	20%
ARF (71)	22%	55%	23%
Required vasopressors (46)	20%	59%	20%
CONTROLS (86)	28%	51%	21%

induced hepatotoxicity requiring ITU were studied. ACE gene polymorphisms were determined by standard PCR based techniques. Haplotype frequency was compared with those of 86 racially and geographically matched controls.

Results: These are shown in Table 39.

Genotype frequencies were compared using χ^2 test with Yates correction. No significant association was found.

Conclusion: In patients with paracetamol-induced acute liver failure there is no association between survival, ARDS, ARF or vasopressor requirement with ACE gene polymorphisms.

Keywords: liver, failure

Serial plasma procalcitonin levels in patients requiring admission to liver ITU with paracetamol induced acute liver failure

N. Jackson[1], S. Batouche[2], R. Sherwood[2] and J. Wendon[1]

[1]*Institute of Liver Studies and* [2]*Department of Clinical Biochemistry, Kings College Hospital, Denmark Hill, London SE5 8RX, UK*

Introduction: Patients with paracetamol-induced acute liver failure have a clinical state resembling septic shock. There is a high frequency of bacterial infection in these patients contributing to the development of multiorgan failure. In the normal liver, Kupffer cells play a major role in clearing bacteria from portal blood. The usual signs of sepsis cannot be used to differentiate between severe hepatic necrosis and bacterial infection.

Procalcitonin (PCT) has been reported to be a selective inflammatory marker that rises in bacterial infection but not in non-infection related inflammation. Possible sources of PCT include monocytes and hepatocytes. We hypothesised that levels of PCT might assist in the differentiation of bacterial infection from toxic inflammatory insult.

Table 40 Procalcitonin and inflammatory markers in acute liver failure *Significant $P<0.05$

Spearman rank correlation		**Mann–Whitney test**	
PCT *vs* APACHE11	$P = 0.0280^*$	admission APACHE 11 *vs* survival	$P = 0.0192^*$
PCT *vs* INR	$P = 0.2471$	admission PCT *vs* survival	$P = 0.5116$
PCT *vs* AST	$P = 0.9913$	PCT *vs* +ve micro	$P = 0.8787$
PCT *vs* CRP	$P = 0.0942$		
CRP *vs* APACHE 11	$P = 0.1271$		
CRP *vs* AST	$P = <0.001^*$		

Method: Serial plasma PCT was measured daily, using a chemiluminescent immunoassay assay in 22 patients admitted with PIALF until either day 5 or discharge and levels compared with APACHE 11 scores, conventional inflammatory markers, liver function tests and microbiological cultures.

Results: From a total of 22 patients 11 survived with medical support alone and 11 did not (seven died, four received liver transplants). A total of 35 blood, 15 urine, 16 sputum cultures were prepared: four endotracheal sputum cultures were positive. Eighty-one daily plasma samples were collected for PCT measurement (Table 40).

Upon admission the following results were obtained: APACHE 11 (4–34) median 19; PCT (1.7–72.1) median 10.6 ng ml^{-1}; INR (2–>15) median 3.6; AST (151–17080) median 8726 IU $litre^{-1}$.

PCT in non-infected patients was (0.9–123.8) median 9.4 ng ml^{-1}. PCT on day of positive culture was (2.3–72.2) median 42.9 ng ml^{-1}.

Conclusion: In patients with paracetamol-induced acute liver failure PCT is significantly higher than in normal controls and correlates with daily APACHE II score independently of the severity of liver insult, however, admission PCT does not correlate with survival. PCT did not specifically rise in those patients who developed chest infection and therefore does not appear to be a useful marker of bacterial infection in this group of patients.

Keywords: liver, failure

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Correspondence

Effect of omitting regular ACE inhibitor medication before cardiac surgery on haemodynamic variables and vasoactive drug requirements

Editor—Pigott and colleagues have addressed the important issue of the influence of ACE inhibitors on haemodynamic variables and vasoactive drug requirements in patients undergoing coronary artery bypass grafting (CABG).[1] Their study is particularly timely because of the increasing trend towards total arterial revascularization for CABG with its superior clinical and survival benefits.[2] In these patients, the need for vasoconstrictor therapy may induce arterial graft spasm and subsequent myocardial hypoperfusion in the postoperative period.

Consequently, it is my current practice to discontinue ACE inhibitor therapy 1 week before surgery in such patients, because of the real, albeit infrequent, occurrence of 'catastrophic' vasodilatory shock requiring vasoconstriction therapy.[2] On the other hand, it seems that the major disadvantage of discontinuing ACE inhibitor medication before CABG, is an increased requirement for vasodilatory medication to control blood pressure in the postoperative period.

In Pigott and colleagues' rigorous and well-conducted randomized trial of 40 patients with good left ventricular function undergoing CABG, 20 patients had ACE inhibitor medication discontinued on the day before surgery and 20 patients were maintained on ACE inhibitor therapy until the day of surgery. Analysing differences in haemodynamic variables and vasoactive drug requirements in the two groups, the authors conclude, 'omitting ACE inhibitors before surgery did not have sufficient advantage to be recommended routinely'.

In fact, the data presented in Tables 2 and 3 may suggest the opposite. Table 2 shows that patients who continued on ACE inhibitor medication required significantly more metaraminol during anaesthesia and in the early postoperative period. Table 3 showed that 65% of patients who had continued with ACE inhibitor therapy until surgery required vasoconstrictor or inotropic therapy in the postoperative period as compared to 35% of those who had omitted ACE therapy the day before surgery (Chi-squared test $P<0.05$).

Two other important points in the study design merit consideration: (i) if the patients who discontinued ACE medication had done so even earlier, the differences between the groups might have been even more dramatic; (ii) only patients with good ventricular function were studied. The potential for ACE inhibitors to cause vasodilatory shock after cardiac surgery, particularly in patients with poor ventricular function, is well recognized.[2]

Pigott and colleagues are to be congratulated on a timely and pertinent study. Their conclusions should, however, be interpreted cautiously in patients undergoing arterial revascularization and particularly so in the presence of impaired ventricular function. While there is clear evidence that ACE inhibitors can cause/precipitate severe haemodynamic disturbances after CPB, I am unaware of any evidence showing a deleterious effect of their discontinuation for a week prior to CABG.

D P. Taggart
Oxford, UK

1 Pigott DW, Nagle C, Allman K, Westaby S, Evans RD Effect of omitting regular ACE inhibitor medication before cardiac surgery on haemodynamic variables and vasoactive drug requirements. *Br J Anaesth* 1999; **83**: 715–20

2 Argenziano M, Chen JM, Choudri AF, *et al.* Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. *J Thorac Cardiovasc Surg* 1998, **116**: 973–80

Editor—Thank you for the opportunity to reply to Mr Taggart's letter in which he raises concerns regarding our conclusion that 'ACE inhibitor therapy, in patients with good ventricular function, need not be routinely discontinued before cardiac surgery'.[1] He raises the issue in the context of patients with poor ventricular function and the increasing trend towards total arterial revascularization where exogenous vasoconstrictor may cause spasm of the conduit. We fully agree with him that our advice may not apply to patients with poor left ventricular function. Our study was only on patients with good or mildly impaired ventricular function. Therefore, we cautioned that the findings of our study may not have been representative of all patients on ACE inhibitor therapy.

Unfortunately, we disagree with his analysis of our data. In our study of 40 patients, those who had continued their ACE inhibitor medication certainly needed more metaraminol during cardiopulmonary bypass (CPB) than those who had omitted their medication. However, in the immediate bypass period, three patients (15%) in the group who continued with an ACE inhibitor needed vasoconstrictors, compared to one patient (5%) in the omitted group. By the time they were in the recovery room the same number of patients in each group (15%) were needing vasoconstrictors. We therefore did not find a statistical difference in the use of vasoconstrictors in the post-bypass and early recovery period between the two groups.

We share Mr Taggart's concerns that exogenous vasoconstrictors may precipitate spasm in arterial grafts, and agree that they should be avoided if at all possible. We are less sure of the role of endogenous vasoconstrictors in the genesis of conduit spasm. Cardiopulmonary bypass is a potent stimulator of angiotensin II production. In our study, the patients who omitted their ACE inhibitor medication had significantly higher systemic vascular resistances in the postoperative period, in spite of large doses of vasodilators. It could be postulated that abrupt discontinuation of ACE inhibitors contributed to vasoconstriction in the postoperative period, possibly with the potential to compromise a radial artery conduit.

It could be that if patients had discontinued their medication earlier, the differences between the groups may have been bigger We understood that common clinical practice was to omit the ACE inhibitors the day before surgery, possibly as this is more likely to be a period where an anaesthetist has control over a patient's medication. We, as yet, do not know the time course for vascular reactivity to return to normal after cessation of chronic ACE inhibitor therapy.

Current anaesthetic practice is to continue with cardiovascular medication up to and including the day of surgery. Before deviating from this accepted norm there needs to be evidence that stopping ACE inhibitors is beneficial. It is of note that, in our study, omitting ACE inhibitors did not prevent three patients from needing vasoconstrictors in the postoperative recovery period. ACE inhibitors are now regarded as the cornerstone of treatment in left ventricular failure. They have consistently shown beneficial

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effects on mortality, morbidity and quality of life in large scale prospective studies.[2] They may also have beneficial effects in preserving regional perfusion and protecting against ischaemia during cardiac surgery.[3] Abrupt discontinuation of ACE inhibitors has been noted to give rise to an increase in ischaemia related events.[4] We therefore did not feel that stopping ACE inhibitors was warranted before cardiac surgery in patients with moderate or good ventricular function. We do, however, recognize the association between poor ventricular function, ACE inhibitors and vasodilatory shock after CPB, and further studies are needed to assess the beneficial effects or otherwise of stopping ACE inhibitors in those patients with poor ventricular function.

D. W. Pigott
Oxford, UK

1 Pigott DW, Nagle C, Allman K, Westaby S, Evans RD. Effect of omitting regular ACE inhibitor medication before cardiac surgery on haemodynamic variables and vasoactive drug requirements. *Br J Anaesth* 1999; **83**: 715–20
2 Davies MK, Gibbs CR, Lip GYH. ABC of heart failure. Management diuretics, ACE inhibitors, and nitrates. *BMJ* 2000; **7232**: 428–31
3 Colson P. Angiotensin-converting enzyme inhibitors. In. Jones RM, Aitkenhead AR, Foex P, eds. *Clinical Cardiovascular Medicine in Anaesthesia*. BMJ Publishing Group, 1997; 52–73
4 Konstam MA, Rousseau MF, Kronenberg MW for SOLVD Investigators. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. *Circulation* 1992; **86**: 431–8

The causes of aspiration pneumonia in mechanically ventilated patients; a possible pathological link with upper airway bacterial colonization

Editor—Allaouchiche and coworkers demonstrated that Gram stain of bronchoalveolar lavage (BAL) fluid was useful for rapid diagnosis of ventilator-associated pneumonia (VAP) in patients undergoing mechanical ventilation.[1]

However, there is a lot of evidence to suggest that pharyngeal bacterial colonization, upper airway bacteria and microaspiration of gastric contents are also important in the development of aspiration pneumonia in mechanically ventilated patients. It has been reported that even a smaller size of nasogastric tube does not prevent or reduce gastroesophageal reflux (GER) or microaspiration in mechanically ventilated patients in the semirecumbent position.[2] A GER and subsequent microaspiration of gastric contents into the lower airways may increase the risk of nosocomial pneumonia. The prevention and detection of pharyngeal colonization are very important in the care of intubated patients in critical care units. The passage of tubes through the nostrils into the stomach may increase the risk of developing aspiration pneumonia. It has been reported that the mean radioactive count of pharyngeal aspirates, but not tracheal aspirate, is greater than the baseline count in mechanically ventilated patients. That is why oral hygiene and airway care are important in preventing the occurrence of pneumonia in intubated patients.[3] In addition, a recent study suggested that the treatment of nosocomial sinusitis decreased the occurrence of nosocomial pneumonia in nasally intubated patients undergoing prolonged mechanical ventilation.[4] Another important factor implicated in the pathogenesis of aspiration pneumonia, is disturbed consciousness due to the use of sedatives.[5] [6] A possible pathological link between upper airway bacterial colonization and aspiration pneumonia should be considered in the diagnosis and/or treatment of ventilator-associated pneumonia. Taken together, the Gram stain of pharyngeal lavage and BAL fluid may be more useful in diagnosing VAP than the stain of BAL alone.

S Teramoto
Japan

1 Allaouchiche B, Jaumain H, Chassard D, Boulétreau P. Gram stain of bronchoalveolar lavage fluids in the early diagnosis of ventilator-associated pneumonia. *Br J Anaesth* 1999; **83**: 845–9
2 Ferrer M, Bauer TT, Torres A, *et al.* Effect of nasogastric tube size on gastroesophageal reflux and microaspiration in intubated patients *Ann Intern Med* 1998; **130**: 991–4
3 Rello J, Sonora R, Jubert P, *et al.* Pneumonia in intubated patients: role of respiratory airway care. *Am J Respir Crit Care Med* 1996; **154**: 111–5
4 Holzapfel L, Chastang C, Demingeon G, *et al.* A randomized study assessing the systemic search for maxillary sinusitis in nasotracheally mechanically ventilated patients. *Am J Respir Crit Care Med* 1999; **159**: 695–701
5 Teramoto S, Matsuse T, Oka T, *et al.* Investigation of effects of anesthesia and age on aspiration in mice using LacZ gene transfer by recombinant E1-deleted adenovirus vectors. *Am J Respir Crit Care Med* 1998; **158**: 1914–9
6 Teramoto S, Matsui H, Ohga E, Ishii T, Matsuse T, Ouchi Y. A novel model of aspiration in young and old guinea pigs using LacZ gene transduction of adenovirus vector. *Br J Anaesth* 1999; **83**: 296–301

Editor—We appreciate Dr Teramoto's remarks. To our knowledge, no studies exist on the reliability of the Gram stain of a pharyngeal sample for the diagnosis of ventilator-associated pneumonia (VAP). The purpose of our work was not to study the pathophysiology of VAP, but to assess the reliability of Gram stain for an early diagnosis. Recently, Cardenosa Cendrero showed that the initial site and route of colonization might not be the same for all microorganisms.[1] The site of colonization is not always the oropharynx and Bonten found in a study of 64 patients[2] that among 20 isolates obtained at bronchoscopy from 11 patients with VAP, 17 (85%) were identified by preceding or concomitant tracheal aspirate, 10 (50%) by oropharyngeal swab, and six (30%) by gastric aspirate. De Latorre[3] found that only 10 of the 21 microorganisms isolated in VAP had previously colonized the pharynx or stomach. In other words, we are not convinced of the usefulness of oropharyngeal sampling.

B. Allaouchiche
D. Chassard
Department of Anaesthesia and Critical Care
Hôpital de l'Hôtel Dieu
Lyon, France

1 Cardenosa Cendrero JA, Sole-Violan J, Bordes Benitez A, *et al* Role of different routes of tracheal colonization in the development of pneumonia in patients receiving mechanical ventilation *Chest* 1999; **116**: 462–70
2 Bonten MJ, Gaillard CA, van Tiel FH, Smeets HG, van der Geest S, Stobberingh EE. The stomach is not a source for colonization of the upper respiratory tract and pneumonia in ICU patients. *Chest* 1994; **105**: 878–84
3 de Latorre FJ, Pont T, Ferrer A, Rossello J, Palomar M, Planas M. Pattern of tracheal colonization during mechanical ventilation. *Am J Respir Crit Care Med* 1995; **152**: 1028–33

Comparison of low dose epidural with combined spinal-epidural analgesia for labour

Editor—We wish to congratulate Dresner and his colleagues on the completion of such a large study and complement them on managing to follow up almost 95% of their population.[1] In 1999, with increasingly early discharges, we managed to follow up a much less impressive 80% out of just over 1800 epidural recipients.

Whilst the authors have demonstrated that there were no clear advantages for either technique, this is only true as long as one is not trying to establish analgesia in late labour with a low-dose mixture. The authors recognize this, in that they withdrew 28 patients from the epidural group because an epidural was 'clinically inappropriate'. If these patients had been given epidurals and they had achieved inadequate analgesia then the proportion of inadequate analgesia in the epidural group would have been 6.6% and not the observed 1.2%. This result would have been significantly more than the 0.4% in the CSE group.

When the CSE technique was first used in labour at Queen Charlotte's Hospital in 1989,[2] it was designed specifically for rapid onset analgesia in women who needed it. The original mobile epidural technique used at that hospital[3] was very similar to the epidural technique used in Dresner's study and did not use a CSE. It was because the original mobile epidural technique gave poor perineal analgesia if started in late labour, that the rapid onset CSE technique already in use at that hospital was adapted to improve the 'mobile epidural'.[4 5]

The analgesic requirement of each mother will vary according to the stage of labour she has reached, and a rapid onset spinal component, as the authors admit, has a role in providing pain relief especially in late labour. It is important to recognize this in any debate on which technique is more appropriate.

At Kingston Hospital in 1999, we identified 42 women out of 1839 epidural insertion (2.3%, 95% confidence interval 1.6–3%) who delivered before the epidural had taken effect. It could be argued that these women should have had a CSE. An additional 60 women received a CSE in late labour to achieve rapid analgesia (3.3%). From these figures we believe that about 6% of women in labour at our institution would benefit from a rapid onset spinal technique.

R G W. Stacey
A. Poon
Kingston Hospital
Kingston upon Thames
Surrey, UK

1 Dresner M, Bamber J, Calow C, Freeman J, Charlton P. Comparison of low-dose epidural with combined spinal-epidural analgesia for labour. *Br J Anaesth* 1999; **83**. 756–60
2 Stacey RG, Watt S, Kadim MY, Morgan BM. Single space combined spinal-extradural technique for analgesia in labour. *Br J Anaesth* 1993; **71**· 499–502
3 Kadim M, Plaat F, Royston P, Morgan B. Mobile epidural analgesia in labour (abstract). Obstetric Anaesthetists Association Spring Meeting. Hereford, 1993
4 Kadim M, Plaat F, Stacey RGW, *et al.* Evolution of the mobile regional technique for analgesia during labour (poster). Obstetric Anaesthetists Association Spring Meeting. Hereford, 1993
5 Collis RE, Baxandall ML, Srikantharajah ID, *et al.* Combined spinal epidural analgesia with ability to walk throughout labour. *Lancet* 1993; **341**: 767–8

Editor—We are grateful for Drs Stacey and Poon's interest and kind remarks about our paper. Whilst not challenging our conclusion that CSE has no advantage over epidural for routine analgesia in labour, they maintain that CSE has a clear role to play in providing rapid analgesia in advanced labour. However, their interpretation of our results to support this assertion is based on assumption rather than hard evidence. Secondly, a more recent study by Nickells and colleagues refutes the claim that CSE provides more rapid analgesia by showing a non-significant advantage of only 2 min over the epidural route.[1] It seems, therefore, that there is no clear evidence to support Stacey and Poon's opinion.

However, we happen to completely agree with them, which is why we still use CSE in 20% of our cases despite the apparent anti-CSE stance of our paper. Whilst Nickells and colleagues' comparison of mean onset times seems to show little speed advantage with the spinal route, mean results fail to reveal that some women experience almost immediate analgesia with a spinal. This virtually never happens with an epidural.

Secondly, Nickells and colleagues define onset times from the moment of drug administration. If time zero is taken from the moment the anaesthetist enters the patient's room, and our two needle technique is used rather than the slower needle through needle approach, we have no doubt that a spinal produces quicker analgesia. With the difficulty of designing a blinded study to negate our obvious bias, it is doubtful if we, or Stacey and Poon, will ever be able to prove this point!

M. Dresner
J Freeman
Leeds General Infirmary
Leeds, UK

1 Nickells JS, Vaughan DJA, Lillywhite NK, Loughnan B, Hasan M, Robinson PN Speed of onset of regional analgesia in labour: a comparison of the epidural and spinal routes. *Anaesthesia* 2000; **55**: 17–20

Alternatives to succinylcholine at Caesarean section

Editor—We read with interest the paper by Abouleish and colleagues[1] which adds to the debate amongst obstetric anaesthetists on the choice of neuromuscular blocking drugs during Caesarean section.[2] It is clear that there are a number of conditions in which the use of succinylcholine is contraindicated. It is not, however, clear what the best alternative airway strategy should be Rapacuronium achieves comparable intubating conditions at 60 s to succinylcholine, but this useful onset time is at the expense of a prolonged recovery from neuromuscular blockade. Although the authors raise the possibility of shortening recovery time by neostigmine administration, this is unconfirmed. In our opinion rapacuronium, because it lacks the important safety features of a quick recovery, is not the best alternative to succinylcholine in this setting. In our institution, when dealing with Caesarean sections under general anaesthetic in women for whom succinylcholine is contraindicated, a propofol and alfentanil technique is used. Intubation without a neuromuscular blocking drug has been validated in a number of studies in the non-obstetric population[3–5] and we have found it successful in this small group of patients. Intubating times and conditions are comparable to succinylcholine and this method scores over rapacuronium by having the option of reversing opiate induced apnoea with naloxone should airway problems be encountered. Abouleish and colleagues have demonstrated that rapacuronium may be the best non-depolarizing agent to use but we suggest that it might not be the best alternative to succinylcholine for the potentially hazardous intubation of a pregnant woman at term.

S. J Young
A. Kilpatrick
Department of Anaesthetics
Glasgow Royal Maternity Hospital
Glasgow, UK

1 Abouleish EI, Abboud Ts, Bikhazi G, Kenaan CA, Mroz L, Zhu J, Lee J. Rapacuronium for modified rapid sequence induction in elective Caesarean section: neuromuscular blocking effects and safety compared with succinylcholine and placental transfer. *Br J Anaesth* 1999; **83:** 862–7
2 Levey DM, Cooper G. Controversies: non-depolarising neuromuscular blockers can be used routinely instead of suxamethonium at induction of general anaesthesia for caesarean section. *Int J Obstetric Anaesth* 1999, **8:** 266–72
3 Beck GN, Masterson GR, Richards J, Bunting P. Comparison of intubation following propofol and alfentanil with intubation following thiopentone and suxamethonium. *Anaesthesia* 1993; **48:** 876–80
4 Alcock R, Peachey T, Lynch M, McEwan T. Comparison of alfentanil with suxamethonium in facilitating nasotracheal intubation in day case anaesthesia. *Br J Anaesth* 1993; **70:** 34–7
5 Scheller MS, Zornow MH, Saidman LJ. Tracheal intubation without the use of muscle relaxants: a technique using propofol and varying doses of alfentanil. *Anaesth Analg* 1992; **75:** 788–93

Editor—Thank you for referring to me the comments of Drs Young and Kilpatrick. Their approach to intubation seems to be a good alternative to succinylcholine. It would be interesting if they could publish a large series in a randomized fashion comparing this technique, namely propofol and alfentanil, with thiopental and succinylcholine in Caesarean section. I hope in their report, the intubating conditions as well as the maternal and neonatal effects would be considered. A physician blinded to the used induction agents should perform the evaluation.

E Abouleish
Department of Anesthesiology
UT-Houston Medical School
Houston
Texas, USA

Anaphylaxis to rocuronium

Editor—A 77-year-old woman presented for cataract surgery under general anaesthesia. She had a medical history of stable angina and asthma (not requiring hospital admission), a hiatus hernia and occasional blackouts Her medications consisted of diltiazem and aspirin tablets, glyceryl trinitrate spray and salbutamol and beclomethsone dipropionate inhalers. She had undergone previous uneventful general anaesthetics including one for cholecystectomy in 1990 during which she received thiopental, atracurium and fentanyl. She thought she might be allergic to penicillin.

Induction of anaesthesia was performed with alfentanil 1 mg, thiopental 250 mg and rocuronium 35 mg. She immediately developed hypotension which did not respond to ephedrine 6 mg i.v. followed rapidly by bronchospasm and tachycardia, and culminating in an electromechanical dissociation cardiac arrest. A further dose of ephedrine was rapidly administered (a total of 24 mg) while epinephrine was being prepared and cardiopulmonary resuscitation was instituted. A blanching rash was noted on the chest wall. The cardiac output was restored after about 5 min and immediately following a third bolus of i.v. epinephrine 1 mg. Haemaccel 1 litre, hydrocortisone 200 mg and chlorpheniramine 10 mg were also administered. She was admitted to the intensive care unit where she received cisatracurium 20 mg to facilitate central venous cannulation and replacement of the tracheal tube by one with a low pressure, high volume cuff. There were no documented ill-effects. Her trachea was extubated 3 h later. She complained initially of chest pain which was thought to be musculoskeletal in origin and, despite developing a chest infection, made a full recovery.

The total IgE on the day of the reaction was 62.1 kU litre^{-1} (80% of normal people have levels of less than 100 kU litre^{-1}). Specific IgE antibodies for latex and succinylcholine were negative. The MAST cell tryptase levels at 30 min, 5 h and the morning following the incident were 118 ng ml^{-1}, 101 ng ml^{-1} and 13.4 ng ml^{-1} respectively (normal range 2–14 ng ml^{-1}). Duplicate skin tests 11 weeks later were negative for latex, vecuronium, atracurium, thiopental, alfentanil and fentanyl, but marked reactions to rocuronium were noted.

The results were discussed with the consultant allergist who investigated the patient. Although the total IgE was not elevated, to exclude an allergic cause the level should be less than 7.5 kU litre^{-1}.

The patient had not received rocuronium previous but cross-reactivity between neuromuscular blocking drugs is not uncommon.[1] However, skin tests for atracurium and vecuronium were negative. These results suggest that the patient had either an anaphylactic or anaphylactoid reaction to rocuronium. Increased mast cell tryptase concentrations are suggestive of an immune cause but may reflect direct histamine release.[2] Other tests including ECG, 24-h ECG, echocardiography, lung function tests and chest radiograph showed occasional ventricular and supraventricular ectopics on the 24-h ECG, cardiac enlargement and mild aortic and mitral regurgitation but no evidence of a myocardial infarction.

The patient was re-listed to have the surgery under local anaesthesia. This case supports the recommendation by Neal and co-workers that the frequency of reaction to rocuronium needs to be monitored.[3]

T. Donnelly
Department of Anaesthesia
Royal Liverpool University Hospital
Liverpool, UK

1 Fisher MM, Merefield D, Baldo B. Failure to prevent an anaphylactic reaction to a second neuromuscular blocking drug during anaesthesia. *Br J Anaesth* 1999; **82:** 770–3
2 Fisher MM, Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. *Br J Anaesth* 1998; **80:** 26–9
3 Neal S McD. Manthri PR, Gadiyar V, Wildsmith JAW. Histaminoid reactions associated with rocuronium. *Br J Anaesth* 2000, **84:** 108–11

Asystole with propofol and remifentanil

Editor—We wish to describe a case of asystole in an adult during a TIVA-TCI induction with remifentanil and propofol. A 52-yr-old obese woman was admitted to hospital for elective cervical spine surgery. Her past medical history was unremarkable; she had no associated diseases, no previous surgery or anaesthetic exposure. Preoperative ECG was normal showing a sinus rhythm of 72 beat min^{-1}. No premedication was given and before anaesthesia the heart rate (HR) and arterial pressure were 80 beat min^{-1} and 120/70 mm Hg respectively. Following atropine 0.2 mg and O_2 100% via a facemask for approximately 4 min, remifentanil was started at 0.25 μg kg^{-1} min^{-1}. Five minutes later, remifentanil was increased to 0.5 μg kg^{-1} min^{-1} and a propofol TCI with a target plasma concentration of 2.0 μg ml^{-1} was started.

Loss of consciousness occurred within 130 s when the calculated propofol concentration was 1.2 $\mu g\ ml^{-1}$ and the total dose administered was 0.36 $mg\ kg^{-1}$. Rocuronium 50 mg was given Arterial pressure and HR during induction fell to 100/60 mm Hg and 55 beat min^{-1} and atropine 0.2 mg was administered. Two minutes later, with a propofol concentration of 1.96 $\mu g\ ml^{-1}$ (total dose 0.75 $mg\ kg^{-1}$), laryngoscopy was started, but before the patient was intubated, the HR rapidly decreased to 32 beat min^{-1}, and, shortly thereafter, asystole occurred. A precordial thump and atropine 0.6 mg restored the sinus rhythm to 50 beat min^{-1} and the arterial pressure to 90/90 mm Hg. The patient was manually ventilated and the Sp_{O_2} rose to 99–100% and the HR to 70 beat min^{-1}. After 1–2 min, a second laryngoscopy was attempted, and another episode of asystole occurred that again responded to a precordial thump and atropine 1 mg. All drug infusions were therefore stopped and after another 2 min, with a heart rate of 80 beat min^{-1} and arterial pressure at 110/60 mm Hg, a third attempt at laryngoscopy and intubation was successful The remainder of the case, including the postoperative course, was uneventful.

The TIVA-TCI technique with remifentanil and propofol has been described as an effective anaesthetic regimen, allowing rapid control of intraoperative stresses in a variety of surgical procedures, including attenuation of haemodynamic responses to tracheal intubation.[1] However, during propofol anaesthesia, a low heart rate may occur despite a decreased arterial pressure.[2 3] Reports of profound bradycardia and asystole with the use of propofol in healthy adult patients, despite prophylactic anticholinergics, have been published repeatedly, and independently of its use in bolus or infusion.[4] There is also copious evidence of the potential of remifentanil to cause hypotension, severe bradycardia and asystole,[5–7] possibly through a centrally mediated decrease in sympathetic tone and vagally-induced bradycardia.[8]

Since both episodes of asystole occurred during laryngoscopy and there was a rapid return to sinus rhythm following a precordial thump, a 'reflex' mechanism was possibly the main cause of bradycardia and sinus arrest in this patient However, this case highlights the fact that the combination of remifentanil and propofol might result in an increased susceptibility to the development of severe bradycardia and asystole during laryngoscopy and intubation, even in healthy patients.

F R. Altermatt
H. R. Muñoz
Department of Anaesthesia
Catholic University of Chile
Santiago, Chile

1 Vuyk J, Mertens MJ, Olofsen E, Burm AG, Bovill JG. Propofol anesthesia and rational opioid selection: determination of optimal EC50–EC95 propofol opioid concentrations that assure adequate anesthesia and a rapid return to consciousness *Anesthesiology* 1997; **87**: 1549–62

2 Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J. Effect of propofol anesthesia on baroreflex activity in humans *Anesth Analg* 1987, **66**. 1115–20

3 Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. *Br J Anaesth* 1988, **60**· 3–9

4 Tramèr MR, Moore RA, McQuay HJ. Propofol and bradycardia· causation, frequency and severity *Br J Anaesth* 1997, **78**: 642–51

5 Schuttler J, Albrecht S, Breivik H, *et al*. A comparison of remifentanil and alfentanil in patients undergoing major abdominal surgery *Anaesthesia* 1997, **52**: 307–17

6 Thompson JP, Hall AP, Russell J, Cagney B, Rowbotham DJ Effect of remifentanil on the haemodynamic response to orotracheal intubation. *Br J Anaesth* 1998, **80** 467–9

7 Wang JY, Winship SM, Thomas SD, Gin T, Russell GN Induction of anaesthesia in patients with coronary artery disease a comparison between sevoflurane-remifentanil and fentanyl-etomidate *Anaesth Intens Care* 1999; **27** 363–8

8 Reitan JA, Stengert KB, Wymore ML, Martucci RW. Central vagal control of fentanyl-induced bradycardia during halothane anesthesia *Anesth Analg* 1978, **57**: 31–6

Unintended total spinal anaesthesia with ropivacaine

Editor—Total spinal anaesthesia (TSA) is produced by excessive doses of local anaesthetic and/or erroneous positioning of the patient. The local anaesthetic spreads and blocks the upper part of the spinal cord and the medulla. Such a case is reported following administration of ropivacaine.

A 68-yr-old man, 74 kg, 171 cm tall, ASA II, receiving amlodipine and propranolol (for arterial hypertension), acarbose (for diabetes mellitus type II), simvastatin (for hypercholesterolaemia) and alprazolam (for anxiety and depression) was scheduled for anterior resection of rectum. A combined epidural/light general anaesthesia was planned.

After arterial pressure monitoring, electrocardiography (ECG), Sp_{O_2} and peripheral venous access had been established, the patient was positioned in left lateral decubitus. After skin disinfection and infiltration with 2% lidocaine, the epidural space was located with a 17 G Tuohy needle by the loss of resistance to air technique and an epidural catheter was inserted at the L_2–L_3 level

After repeated aspiration through the Tuohy needle and epidural catheter, when no blood or CSF was obtained, 1% ropivacaine 20 ml was injected over 4 min (no test dose was given). Immediately after finishing the injection, the patient noted loss of strength in the right leg In the next 30 s, there was loss of strength in the right arm followed by asystole, respiratory arrest and loss of consciousness. Escape beats were observed on the ECG Sinus rhythm returned after mask ventilation with oxygen 100%, atropine 1 mg and ephedrine 50 mg. The patient opened his eyes, but as he was apnoeic and paralysed, propofol 1.5 $mg\ kg^{-1}$ and alfentanil 30 $\mu g\ kg^{-1}$ was given, the trachea was intubated and mechanical ventilation was initiated with air/O_2 ($F_{I_{O_2}}$ 0.4) Anaesthesia was maintained with a propofol infusion at 6 $mg\ kg^{-1}\ h^{-1}$.

Suspecting a TSA, repeat aspiration through the catheter yielded a clear fluid, that was sent to the laboratory and confirmed to be CSF as it contained glucose 50 mg% and protein 42 mg%

After 15 min the patient was stabilized cardiovascularly and it was decided to carry on with surgery During the 2 h 25 min of the procedure no more analgesic or muscle relaxant was required Throughout the operation, cardiovascular stability was maintained with small doses of ephedrine, totalling 60 mg. At the end of surgery, the patient recovered consciousness, obeyed simple commands and maintained spontaneous ventilation with a normal Sp_{O_2} and tidal volume He was extubated before being taken to the post Anaesthetic Care Unit (PACU).

In the PACU arm motility was normal, but in the left leg there was a modified Bromage score of 0 and hypoaesthesia. In the right leg Bromage score of 3 and analgesia was noted There was hypoaesthesia of the abdomen. Over the following 8 h, the patient fully recovered from his sensory and motor deficits. After 30 h, the patient left the PACU without any adverse effect. On the fifth postoperative day, neurological examination was normal.

In this report, the catheter, not the needle, entered the subarachnoid space. Nevertheless, repeated aspiration did not obtain CSF or blood, so it can be postulated that a valvular mechanism was involved, allowing passage of the injected local anaesthetic, but no aspiration of CSF This mechanism explains the high incidence of false negative aspiration tests. No test dose was given, but there were no signs of intravascular injection of local anaesthetic. It is probable that with 1% ropivacaine the passage of 1–2 ml of local anaesthetic into the CSF should have show signs of spinal anaesthesia.

In TSA, profound hypotension, severe bradycardia and cardiac arrest are frequent and secondary to the total sympathetic block; respiratory arrest is the result of respiratory muscle paralysis and local anaesthetic action on the respiratory centre of the medulla. Patients without cardiorespiratory pathology will tolerate the massive block if treated promptly. In this case although there was a cardiac arrest, the cardiac rhythm recovered spontaneously, first as an escape rhythm and then as sinus rhythm. Arterial blood pressure also recovered rapidly with ephedrine.

At the end of the procedure, 3 h after injection of the local anaesthetic, the block had receded sufficiently to allow tracheal extubation and maintenance of spontaneous ventilation. After a further 8 h, there were no clinical signs of residual block No neurological deficit could be detected 5 days later, nor transient neurological symptoms as have been repeated with other local anaesthetics such as lidocaine or mepivacaine;[1] nor symptoms derived from ischaemia of the spinal cord, due to any vasoconstrictor effect of ropivacaine.[2]

Spinal anaesthesia with ropivacaine is not recommended by the manufacturers because of a lack of any investigations of its use in this purpose As other local anaesthetic drug administered specially have shown side-effects, such as transient radicular irritation, it is appropriate to be cautious about introducing a new drug for this indication. In experimental animals ropivacaine has been considered useful for spinal anaesthesia.[3] In humans, ropivacaine 15 mg or 22.5 mg[4, 5], or 2–4 mg with sufentanil 10 µg,[6] showed no adverse effects. But administration in hyperbaric solution with 5% glucose of ropivacaine 4, 8 or 12 mg was followed by a higher incidence of back pain than bupivacaine.[7]

J L. Esteban
A Gómez
F Gonzalez-Miranda
Departmento de Anestesiologia y Reanimación
Hospital Universitario de Canarias
Tenerife

1 Hogson PS, Neal JM, Pollor JE, Liu SS. The neurotoxicity of drugs given intrathecally (spinal) *Anesth Analg* 1999; **88**; 797–809
2 Iide H, Watanabe J, Dohi S, Ishiyama T. Direct effects of ropivacaine and bupivacaine on spinal pial vessels in canine *Anesthesiology* 1997; **87**. 75–81
3 Kristensen JD, Karlsten R, Gordh T. Spinal cord blood flow after intrathecal injection of ropivacaine: a screening for neurotoxic effects. *Anesth Analg* 1996; **82**; 636–40
4 van Kleef JW, Veering BT, Burm AG. Spinal anesthesia with ropivacaine: a double-blind study on the efficacy and safety of 0.5% and 0 75% solutions in patients undergoing minor lower limb surgery *Anesth Analg* 1994; **78**; 1125–30
5 Wahedi W, Nolte H, Klein P. Ropivacaine for spinal anaesthesia. A dose-finding study. *Anaesthesist* 1996; **45**: 737–44
6 Levin A, Datta S, Camann WR. Intrathecal ropivacaine for labor analgesia: a comparison with bupivacaine. *Anesth Analg* 1998; **87**; 624–7
7 McDonald SB, Liu SS, Kopacz DJ, Stephenson CA. Hyperbaric spinal ropivacaine: a comparison to bupivacaine in volunteers. *Anesthesiology* 1999; **90**: 971–7

Protecting anaesthetic tubing from occlusion

Editor—We are sure all anaesthetists become frustrated with the limited mobility of modern anaesthetic machines, particularly when the wheels become 'chocked' by the profusion of pipelines, electrical cables and scavenging tubing. Indeed, Dr Carvalho described a case of back-pressure being inadvertently applied to a breathing system following manoeuvring of an anaesthetic machine.[1]

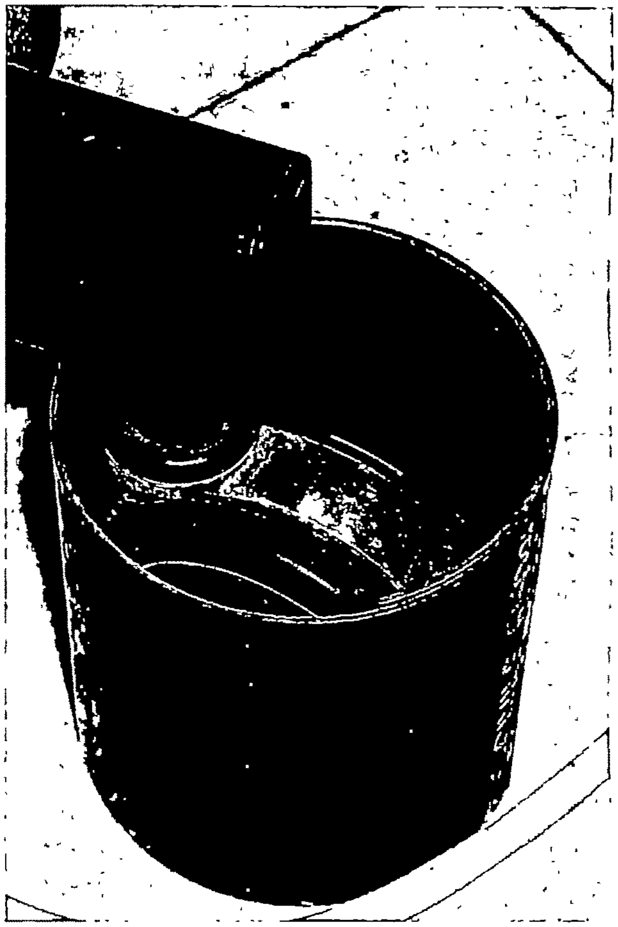

Fig 1 Pipe section in place around rear wheel of the anaesthetic machine

To prevent this problem both cheaply and efficiently, we suggest the following method, which is similar to that used at the Hospital for Sick Children, Toronto.

1. Take a section of 6 5 inch plastic soil pipe, and cut it into 5.5 inch lengths.
2. Split down the longitudinal axis, allowing the cut edges to overlap.
3. Place around the rear wheels of the anaesthetic machine (Fig. 1).
4. Manoeuvre at will.

The pipe sections may be removed for cleaning or when the anaesthetic machine is to be moved over longer distances. Our recommended measurements are for the Ohmeda machine chassis, but may be adapted for other machines. We have adapted all our anaesthetic machines in this way, to universal acceptance.

R Dell
D Cochrane
Directorate of Anaesthesia
North Bristol Hospital Trust (Frenchay)
Bristol, UK

1 Carvalho B. Hidden hazards of scavenging. *Br J Anaesth* 1999; **83**: 532–3

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Book Reviews

The Effective Management of Postoperative Nausea and Vomiting. L. Strunin, D. Rowbotham and A. Miles (editors). Published by Aesculapius Medical Press, London. Price £18.50.

This monograph is one in a series entitled *UK Key Advances in Clinical Practice Series*. The aim of this clinical practice project is to 'catalogue all available scientific evidence and expert opinion for the investigation and management of a wide variety of common disease presentations'. The ultimate goal is to provide clinical practice guidelines for the management of common problems. The series has discussed the effective management of breast, colorectal and ovarian cancers, cancer pain and headache in its previous monographs. It is heartening to note that the Royal College of Anaesthetists decided to focus on postoperative nausea and vomiting (PONV) as an unsolved problem. The remarkable safety record of anaesthesia is well established in the last decade It is therefore most appropriate to concentrate on improving patient experiences in what were once considered unavoidable side effects of surgery—postoperative pain and sickness.

The book has been written by British authors and provides a comprehensive review of the subject from their perspective. As with any multi-authored monograph, there is some variability in the style and quality of writing, along with some repetition, which has been kept to a minimum. The monograph is divided into three sections. In the first section, the epidemiological aspects of the problem are discussed, along with the physiology of the emetic reflex. The chapter on the physiology and mechanisms of PONV is first rate. Dr Andrews brings to our attention the fact that nausea and vomiting are not synonymous, and that nausea may result from a lower level of activation of the emetic pathway, but does require activity from centres higher than the area postrema. An understanding of the mechanism of PONV is essential for its proper management, and the role of gastro-intestinal blood and distension in the aetiology of PONV is discussed. In this chapter, the pharmacological basis for the action of various antiemetic drugs is introduced, emphasizing that no one drug to date will be effective in all situations. Dr Andrews also brings to our attention a new group of drugs—the NK1 antagonists. In animal studies, these drugs reduce emetic symptoms originating from the area postrema, vagal efferents and the vestibular system. The ability to block emesis from three major pathways is exciting, and this group of drugs may prove to be very useful in managing PONV.

The second section provides evidence for pharmacological and non-pharmacological management of PONV. The authors have attempted to put together in one place the many studies available in the literature on this topic. Unfortunately, the older drugs have significant side-effect profiles and evidence for their efficacy is incomplete or based on poorly designed investigations with a lower power to detect differences in the groups studied. An introductory section regarding study design may help future investigators provide the data that are missing in the currently available literature. The authors have also introduced the concept behind the numbers-need-to-treat approach that has been popularized by Tramer. The chapters on pharmacology of PONV appears somewhat dated and the reference list incomplete. It may benefit from inclusion of studies done outside the UK.

The second section also discusses non-pharmacological approaches to the management of PONV with an emphasis on acupuncture, acupressure and acustimulation. These methods are effective but perhaps as adjuncts to other methods. The use of the numbers-need-to-treat approach will put the benefits obtained by this method into perspective for the clinician. The second section also contains a chapter by Professor Rowbotham where he discusses what to do when prophylactic antiemetic therapy has failed. It takes a very common sense, systematic approach to the problems of failure of PONV prophylaxis in an individual patient, and to the problem of a high incidence of PONV detected by an audit. The experience of the author and a well thought out plan is evident. It provides a good link to the next section of the book.

The third section emphasizes the need for a multidisciplinary approach to the management of PONV along the lines used for the management of pain. The first step is to know what is happening in your own institution, and the questionnaire used by Vickers can be used in all institutions. An algorithm and practice guideline is provided in the Appendix This section also discusses the need for further education and research strategies.

Overall, the authors have provided a good basis for the management of PONV. Since the *Clinical Practice Series* project recurs on an annual basis we can look forward to a more updated version. A more detailed discussion of the pros and cons of prophylactic management of PONV *versus* a strategy of treating only those with established symptoms is necessary, along with a formal review of data on the cost-effectiveness and patient satisfaction with these strategies. Ultimately, no practice guideline can cover all situations and an individualization of management based on a given patient's risk is essential. It will take time to establish a consensus on the best practices in managing PONV. The authors of this book should be congratulated on starting this process of examining the evidence. The low cost of the book (£18.50) is attractive for libraries and individual practitioners

M. Watcha

Anaesthesia and Intensive Care A to Z. An Encyclopaedia of Principles and Practice, 2nd Edn. N Hirsch, S Yentis and G. B. Smith. Published by Butterworth–Heinemann, Oxford. Pp. 560; illustrated. Price £45 00. ISBN 0 7506 3249 6.

This is the second edition of a hugely successful reference book, first published in 1993, and subsequently reprinted three times. It is literally an encyclopaedia, containing bite-sized summaries of a huge range of anaesthetic and intensive care subjects, covering all aspects of the FRCA syllabus. The authors have collected and distilled information on thousands of topics, including the history of anaesthesia as well as more mainstream subjects. Each topic is precisely and concisely described, and the text is liberally interspersed with excellent tables and line diagrams. This is well demonstrated by the diagram of the brachial plexus which allows even the most '3D disadvantaged' anaesthetist to navigate the cords logically. The cross referencing, crucial in a book such as this, is clear and logical.

The text assumes a basic understanding of the subject matter, and so is not suitable for the novice trainee. However, for the more senior trainee it is an ideal reference book, and for trainees taking examinations it is second to none. With virtually all the topics pertinent to the FRCA in one book, locating the answer to that difficult MCQ question, or finding the exact formula for the oxygenation index, becomes very easy. The major topics all have references to reviews for in-depth study if needed. This book is an ideal antidote to the pre-examination panic caused by piles of detailed texts littering your desk.

In this second edition, the authors have specifically increased the number of intensive care topics to cover the syllabus of the Intercollegiate Diploma of Intensive Care Medicine, which was developed after the first edition was published The scope of the

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book has also been widened to include topics relevant to intensive care nurses, operating department practitioners and all health care workers allied to anaesthesia and intensive care. As a result, the book has gained another 100 valuable pages since the first edition.

We would recommend this book as an ideal reference text for the trainee undertaking the FRCA examination and as a wonderfully quick reference and aide-memoir for the more senior practitioner. It should be in every anaesthetic department's library. This is a book you would like to be easily available to you during your working day, but sadly it is too big to be 'briefcase friendly'. When is the electronic version going to be available for our Psions?

K. MacLachlan
J. D. Young

Procedures and Techniques in Intensive Care Medicine, 2nd Edn. R. S. Irwin, J. M. Rippe, F B Cerra, F. J. Curley and S. O. Heard. Published by Lippincott Williams and Wilkins, Philadelphia. Pp. 307; indexed; illustrated. Price $US59.95. ISBN 07817 20478.

However effective our training programmes are, good books covering practical procedures are popular. Standard textbooks tend not to dwell on practical matters and 'how to do' things. This book was originally a section of an established textbook of intensive care medicine first published in 1985. It is published separately to make it easier to carry and more accessible to nurses, trainees and specialists from all disciplines of emergency medicine. Now in its second edition, the editors have given attention to modernizing the content

Procedures and Techniques in Intensive Care Medicine is a comprehensive review with each of the 307 pages containing closely typed text occasionally interspersed with line drawings and illustrations The 31 chapters are a collection of mini works by the 45 contributors; some are remarkably detailed. The back cover of the book says 'Carry this handy resource with you for easy-to-follow, step-by-step instructions for every important diagnostic and therapeutic procedure used in adult critical care'. It would be reasonable to assume from this description, and the title, that the book concentrates on practical aspects of intensive care procedures but the reader may be surprised by the wealth of additional information covering the theoretical basis of measurement. For example, the chapter on intra-aortic balloon pumping discusses in detail the different timing methods that can be used, and the chapter on indirect calorimetry has a large section on the theoretical basis of the technique. Reducing some of this extra material would allow the book to be changed in size to one more convenient for use in the clinical area.

Valuable information exists for readers who wish to refer to a section of special interest but the book is variable and there is not really a constant style. Some chapters concentrate more on theory than others and lack of editorial control means there is a lot of repetition. For instance it would be useful to have detailed sections discussing consent in intensive care and the importance of sterile technique rather than allowing many of the authors to mention these issues in a superficial manner.

The hard work of the authors updating the text is obvious but in many cases this appears to have been done by adding a section rather than by a rewrite. The chapter on tracheostomy states 'Although tracheotomy is best performed in the operating room, bedside tracheotomy can be performed safely under certain conditions' Almost as an afterthought later in the chapter, after a discussion of the role of metal tracheostomy tubes, comes a section on 'Percutaneous Airway Technique'. Here the importance, safety and value of the percutaneous techniques are discussed. However, it would have been appropriate to allocate more space to describing how to perform percutaneous tracheostomy, the complications and the ways in which the risk of complications could be reduced. The author seems to deliberately interchange descriptions of tracheostomy and cricothyrotomy (which he says has found particular favour in Great Britain). The reader is told that 'In experienced hands some percutaneous techniques frequently can be performed in only 30 s and usually in less than 2 min.'

Many of the techniques described will not be performed by the average intensive care doctor but are of great interest, such as interventional radiology, extracorporeal oxygenation and cardiac assist devices. But some topics are not relevant such as the chapter on joint aspiration which should be left in the hands of an expert.

Whatever your view about the current role of the pulmonary artery catheter, over the last 30 years it has guided a major change in the way in which intensive care is practised. There is great opportunity in a book of this type to briefly comment upon the current status of the pulmonary artery catheter and why it could improve or worsen outcome Practical detail about the use of this tool is missing. I doubt whether the trainee who is unsure how to interpret a wedged trace, in a patient breathing spontaneously with the occasional ventilator delivered mandatory breath, will be able to find the answer here. Sometimes the authors quote published work but fail to provide the interpretation that should be expected in a text aimed at trainees. The section on 'Anesthesia for Bedside Procedures' recommends etomidate for use in critically ill hypovolaemic patients. One table describes it as having no cardiovascular effects. This sort of information needs considerable qualification before it is translated into patient care. Similarly, remifentanil is also discussed with insufficient clinical detail.

There are differences in the way in which health care is provided on each side of the Atlantic Ocean and the terminology used. In the section on ECG it says 'Continuous ECG monitoring is performed routinely in almost all ICUs in the United States.' Many of the procedures described discuss dealing with problems seen in conscious, unventilated patients. This may be interesting but relates to patients with single system failure rather than the average UK intensive care patient.

I would advise this book be used as a reference text, many of the sections being informative and of value to the experienced reader I would not feel happy recommending it to my trainees as a practical clinical guide.

A. T. Cohen

Principles and Practice of Obstetric Anaesthesia and Analgesia. A. Holdcroft and T. A. Thomas. Published by Blackwell Science, Oxford. Pp. 384; indexed; illustrated. ISBN 08654 828X.

The classic British textbooks of obstetric anaesthesia are now out of date and this one is timely as a new contender to the marker. The layout is traditional though there is a generous use of tables and bullet points within the prose. I had a little difficulty in deciding whether the book was for anaesthetists in training or consultants. The chapters on physiology are detailed and at a level that may overwhelm the SHO, whereas the chapters on regional analgesia and anaesthesia, and general anaesthesia are at a more basic level.

Section one of the book covers the organization of obstetric anaesthetic services and the chapter on maternal mortality is excellent. The second section covers systemic physiology and pathology comprehensively in each of the systems. This section is excellent, well researched and leads into the practical management problems that may be encountered with a pregnant woman suffering from a disease process. It is refreshing to see a chapter on the puerperium, an area that is often forgotten despite our enthusiasm as obstetric anaesthetists to audit long term outcomes of epidural analgesia and anaesthesia. However, it is disappointing that there is no mention of post-traumatic stress which may develop in women where the outcome of labour was poor, the pain relief or anaesthesia was poor, or the delivery itself was traumatic.

The third and fourth sections of the book cover the practise of regional analgesia and anaesthesia and general anaesthesia and are not as detailed as the first two sections. The problem of pain during Caesarean section is dealt with briefly without stressing the importance of good record keeping and follow up for both the mother and the junior anaesthetist. The anatomical illustrations are excellent and are comprehensive in the inclusion of the lumbar sacral plexus, the spinal cord and a good female dermatome chart. I was disappointed that there was no discussion on the effect of epidurals on labour outcome particularly with 'walking epidurals', and a more comprehensive account of the management of the pain of labour without regional analgesia

This book is good on principles but lacking on some of the practical aspects of obstetric anaesthesia. However, it is a book that I would recommend all libraries and obstetric departments to buy and I would encourage those interested in obstetric anaesthesia to read. This is a book that the late Dr Jeffrey Selwyn Crawford would be proud of.

A. E. May

Managing Obstetric Emergencies. C. Cox and K. Grady. Published by Bios Scientific Publishers Ltd, Oxford. Pp. 195, indexed; illustrated. Price £19.95 ISBN 185996 1223.

Emergency obstetric practice is still the domain of SpRs in training and this little pocket book will be welcomed most by those on the front line where the least experienced often have to deal with the most taxing obstetric problems. Written by a consultant obstetrician and a consultant anaesthetist, it is an encouraging sign of the collaboration that now prevails between the two specialities in the labour ward, facilitated no doubt, by a common foe—the lawyer!

Obstetricians are the path finders in evidence based medical practice, and much of the background work for this book was undertaken in the development of evidence based guidelines for the North Staffordshire project 'Achieving Sustainable Quality in Maternity (ASQUAM)' co-ordinated by Richard Johanson, who also contributes several chapters to the book. Over 60 topics are covered in just under 200 pages grouped under the four main headings of Resuscitation, Obstetric Emergencies, Medical Emergencies and Legal Issues, with the emphasis very much on obstetric rather than purely anaesthetic problems. Difficult and unusual problems such as: confusion; HIV and AIDS; the Jehovah's Witness patient; substance abuse; transfusion reactions; and issues of consent, are all here. Particularly valuable is a list of helpful national telephone numbers

An ATLS style action plan is provided for most of the chapters, followed by supplementary information and a synopsis of systematic reviews. The authors acknowledge that this approach inevitably leads to much repetition but believe that it is the safest one for the relatively inexperienced practitioner. They may be correct, and certainly it works well for the resuscitation section but, as a slight ATLS phobe, I was less convinced about this format for some of the other sections. In many chapters, I found the action plans too generalized, whereas the supplementary information was often extremely valuable and informative Management of purely obstetric emergencies such as abnormal presentations, inverted uterus and retained placenta are done well with a clear didactic message. Eclampsia, pre-eclampsia and the diabetic patient are also clear and unambiguous. However, I thought abdominal pain, puerperal sepsis and thromboembolism too generalized and wanted more key diagnostic and therapeutic detail Haemorrhage is comprehensively covered in three chapters and I was pleased that the life-saving procedure of abdominal packing is recommended when all else fails. But I would have liked more specific criteria about when conservative management of postoperative bleeding has failed since 'too little, too late' is still a problem. I shuddered slightly at the recommendation of considering heparinization in the presence of acute DIC and wanted more detail about clotting tests, what they mean and how to act on them. There are very few typographical errors, the book is well indexed and the section on normal values in pregnancy is particularly useful.

The publication of this book coincides with that of the similarly sized new edition of Professor T Baskett's *Essential Management of Obstetric Emergencies* (3rd Edn) which covers far fewer topics but is richer in diagnostic detail. In places such detail is missing from this book and could, with advantage, be introduced into the next edition at the expense of some of the repetitive action plans

This is not a book for the library. It belongs in the white coat of every obstetric SpR as his or her *vade-mecum*. It will also be invaluable as a basis for drawing up and updating multi-disciplinary labour ward protocols

R. G. Wilkes

Handbook of Obstetric Anaesthesia M C. Norris Published by Lippincott Williams and Wilkins, Philadelphia. Pp 529, indexed, illustrated. Price £25.00 ISBN 0781 18597.

This handbook is written by a well-known specialist in obstetric anaesthesia. It is nicely produced and presented as almost 600 pocket-sized pages of text. The jacket recommends it as a portable, practical distillation of Dr Norris's best selling text book It is divided into three parts: (i) pre-operative assessment; (ii) intra operative management; and (iii) after delivery Each part is subdivided into chapters; there are 33 in all. Each chapter is up to date and well referenced. Any diagrams or figures are helpful and clear, as is the subject index at the back of the book. But the 'pocket sized powerhouse' approach to Part I, which includes comprehensive lists of facts on physiology and pre-operative evaluation of the pregnant patient, makes heavy reading of the first six chapters.

Parts II and III have some excellent chapters. Alternatives to conduction analgesia are well presented Interesting statistics are counterpointed with helpful tips on epidural catheter placement A basic yet comprehensive approach is taken to such diverse topics as general anaesthesia, pre-eclampsia, substance abuse. vaginal births after Caesarean section, and complications with regional anaesthesia.

A prudent course of action is suggested for clinical scenarios Careful and thoughtful analysis is given to the grey areas of obstetric anaesthesia and the author is confident in giving his personal recommendations He gives an amusingly common sense approach to ambulation in labour, but I do not believe he meant us to increase the bupivacane concentration to 0.4% as a response (p. 273); he surely meant us to decrease it to 0.04% The North American origin of this book inevitably leads to discussion of drugs not available in Great Britain, with an absence of any reference to diamorphine. Similarly, some units of measurement are specific to the American system.

The price of the book (£25 00) makes it suitable for individual purchase, and it is small enough to fit into a white coat pocket The condensed style of writing, with list format, makes it a book to dip into rather than one to read for prolonged periods

L. Fahy

Anaesthesia for Vascular Surgery. J Bannister and J. A. W. Wildsmith (editors). Published by Arnold, London. Pp. 337; indexed, illustrated Price £55.00 ISBN 0340692049

The editors feel that the expanding role of anaesthetists as members of the perioperative team, becoming more involved in all aspects of surgery including preoperative assessment and optimization, discussion of surgical options in terms of optimal risk benefit, and postoperative care in the Intensive Care or High Dependency Unit has shaped the form of this book. They hope it reflects current best practice. Authors of the 18 chapters are drawn from many parts of the world. Each chapter is comprehensively referenced and they are all up to date. The authors of each chapter are experts in the field and are obviously practising clinicians within their field of expertise. They argue their point of view cogently, and consistently provide logical, balanced guidance on anaesthesia (and its pitfalls) for vascular surgery in the broadest sense. Each chapter manages to present convincing data as to why their point of view is correct. At the same time, they provide the reader with both sides of the argument when the evidence for any opinion is not overwhelming.

The title suggests that this book will only be of value to those anaesthetists practising in the rather limited field of major vascular surgery. However, that is not the case. A number of chapters consider the pathophysiology of vascular disease and assessment and anaesthesia for patients with vascular disease. In view of the increasing amount of surgery being performed on an increasingly elderly population, the book will be useful for any anaesthetist involved in any form of anaesthesia for the elderly, particularly those with established cardiovascular disease. The chapter on preoperative assessment of a patient with cardiovascular disease is one that I think all trainees in anaesthesia and surgery should read thoroughly and commit to memory.

Each part of the body commonly requiring the attention of a vascular surgeon, for instance the descending thoracic aorta, the abdominal aorta, the carotid artery, the lower limb, and the upper limb, and vascular emergencies have a separate chapter in this book. In addition to the more obvious chapters on anaesthesia for the most common vascular surgery operations, there are also chapters on the epidemiology of vascular disease, the scope of vascular surgery, normal cardiovascular physiology, preoperative assessment of all patients at risk of cardiovascular complications, and perioperative management of the cardiovascular system. There is a chapter on anaesthesia for renovascular surgery and renal transplant and finally an analysis of costs *versus* benefit for vascular surgery.

The editors are to be congratulated on the general layout of the book and for ensuring that the prose is readable and understandable while still retaining all the necessary factual information. The book will appeal to any anaesthetist performing vascular surgery on a regular basis as it reminds us of the options and gives a good list of references for further reading It will also appeal to those practising in any field of anaesthesia that involves looking after patients with a compromised cardiovascular system. The chapters on cardiovascular dysfunction, preoperative assessment of the patient at risk of cardiovascular complications, and perioperative management of the cardiovascular system are easy to read and will be immensely useful for any anaesthetist in training. Departmental libraries should consider owning this book and I am sure that all those who acquire a personal copy will consider it money well spent. I can recommend it wholeheartedly.

R. M. Grounds

Pediatric Anesthesia—A Quick Pocket Reference, 2nd Edn. D. C. Bloch and B. Ginsberg. Published by Butterworth–Heinemann, Woburn Pp. 365; indexed. Price £25.00 ISBN 0 7506 7142 4.

This pocket reference book seems to be aimed at American anesthesiology trainees and the occasional pediatric anesthesiologist, who needs to know about drug doses and what to do in certain situations, without much background explanation. Although the authors have European and South African anaesthetic qualifications they now practise in the USA and so this book has a decidedly American slant. Of course, any book that advertises itself for pocket reference has to be able to fit into a pocket, and this one just about does, although it is rather heavy, weighing in at 250 g (9 oz); it would need something like a digital organizer in the opposite pocket to give balance! It has 15 chapters that cover most areas of paediatric anaesthesia, the majority of sections being in alphabetical order. Some of the chapters, such as those on anaesthetic related drugs and maintenance of anaesthesia, are simply lists of drugs, again in alphabetical order, and their doses. The layout of these sections does not make for easy reading as the drug name is on the left one third of the page and information about that drug is rather squashed into the remaining two-thirds of the page. Interestingly, remifentanil is not mentioned anywhere in the book Some of the drugs listed have American proprietary names and doses are in the '× mg/kg q8h' format. A number of other abbreviations will be recognized by ER fans such as D5W (5% dextrose in water). All ions are mEq and not mmol.

The first chapter on preoperative considerations does not mention EMLA or AMETOP, although EMLA does appear in the chapter on local and regional anaesthesia. In the first chapter it is suggested that an oral mixture of pethidine, diazepam and atropine is good for outpatient premedication, which would be considered unusual on this side of the Atlantic Ocean. What is included in which chapter is quite novel in some instances, and does lead to surprises, but makes the book somewhat difficult to navigate. For instance, Chapter 4 is called 'Reversal' and this includes reversal of anything that is normally, or can be, reversed; such as neuromuscular blockade, warfarin or respiratory depression! Epiglottitis is included in the chapter on perioperative problems, rather than the airway chapter. The airway chapter does not describe how to manage a difficult airway, but does give a list of syndromes that are associated with difficult intubation.

There are a number of helpful appendices at the end of the book ranging from normal paediatric values, to SI units and conversion factors, to definitions of various physical laws and equations There are also sections on proprietary names, all American, with their generic equivalents, and a large section of over 40 pages on syndromes and their anaesthetic implications. The last appendix is a list of nearly 400 references for the entire text, which is almost up to date, the most recent being from 1998. There are no illustrations in the book, which is presumably to keep its size to a minimum, but resuscitation algorithms are included. Two to four useful blank pages for additional reader's notes are found at the end of each chapter.

So, if one of my trainees asked me to recommend a smallish book on paediatric anaesthesia would I suggest this one? Probably not, as I would suggest foregoing the convenience of the pocket-sized book for a book which was more explanatory and easier to read.

A. R. Bowhay

Clinical Pharmacology of Local Anaesthetics. J. E. Tetzlaff. Published by Butterworth–Heinemann, Boston. Pp. 258; indexed; illustrated. Price £36.99 ISBN 0 7506 9797 0.

Although American in origin, readers outside the USA will find this well-written book relevant; the local anaesthetics that are available in different parts of the world are described with frequent references to alternative drug names and spellings. Bold type is used throughout to highlight key terms, and the text is well referenced for further reading. Many illustrations complement the text but unfortunately they look untidy because they have been sketched rather than drawn formally. A soft cover book, it is divided into five main sections with a total of 38 short chapters.

The first section comprises seven comprehensive chapters on the basic physiology and pharmacology (including systemic toxicity and allergic reactions) of conduction blockade. The chapter on allergy gives a very clear description of the pathophysiology of anaphylactic and anaphylactoid reactions and outlines strategies, both current and those in development, for identifying the allergen. There is little to disagree with in this section, but the brevity of some of the chapters has not allowed clear definition of some key terms (e.g. frequency-dependent blockade).

The second and third sections discuss the individual agents, first the esters then the amides. Using an identical format, each chapter deals with a single agent and encompasses history, chemical formulations, properties, toxicity and the application of the particular agent to clinical practice. A short section dealing with any controversy regarding the agent is also included. For example, the chapter on lidocaine considers the aetiology of the transient neurological symptoms that have been described after its intrathecal use. The standard chapter structure is very useful for those wanting detailed information on a particular agent, but there is a lot of repetition between chapters as each agent is considered individually for all forms of regional technique.

The fourth section, additives and compounds, looks at strategies used to improve the clinical action of the various agents, and also the use of mixtures of local anaesthetics. Vasoconstrictors, EMLA and the chemical manipulation of agents are covered. There is an interesting chapter on compounding of local anaesthetics looking at the controversy of whether mixtures of agents cause synergistic or additive toxicity. The author quite rightly states that there is no evidence to support either theory in man and that the evidence from animal models is both confusing and contradictory.

The final section of the book deals with the surgical application of local anaesthetics and although comprising approximately a third of the book, is the least well written. The author has given each surgical specialty for which local anaesthetic techniques can be used a separate chapter. Within each, the more common operative procedures are outlined, but rather than dealing with the basic principles, individual procedures are considered briefly and to the detriment of the content. Also, in including the more obscure practices (e.g. the use of spinal anaesthesia for cardiac surgery; intraperitoneal infusions to decrease ileus after bowel surgery) the author has not covered routine practice thoroughly. In a text of this nature, aimed primarily at the trainee anaesthetist, the more common techniques should be described thoroughly and the obscure left to more comprehensive texts.

In summary, this is a well researched, up to date text which is very easy to read and which would be of use not only to the trainee preparing for examinations, but also to any anaesthetist with an interest in regional anaesthesia. The final section is disappointing, but the comprehensive content of the other sections more than compensates for it. I feel this book would be a useful addition to any anaesthesia departmental library.

J. B. Whiteside

British Journal of Anaesthesia **84** (5) 703 (2000)

Erratum

Malposition of the epiglottis after tracheal intubation via the intubating laryngeal mask (BJA 1999; 83: 962–3)

In Figure 2 the arrow pointing to the laryngeal aperture should have been labelled pyriform fossa.

Putting the sterile syringe packaging to good use (BJA 2000; 84: 127)

The size of the syringes was incorrect in second sentence in the second paragraph. The correct sentence is given below. The publisher apologises for this error.

The plastic sterile packaging of the 20- and 50-ml syringe should be cut or torn neatly at the end opposite to the plunger.

Guide to Contributors

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Dr J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005.

Papers

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publisher.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki and should normally include a statement of approval from an appropriate Ethics Committee. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted. Studies from the UK should specify the Home Office Licence number; from elsewhere, a statement of approval from an appropriate licensing authority.

Legal considerations

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Preparation of manuscript

Four copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss. Where possible, manuscripts should also be submitted on disk. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the three other sets may be photocopies.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all the authors. There should be a clear declaration of any financial or commercial interest which any author may have in the material. The Editor may wish to see raw data if necessary.

Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary, including Keywords
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Illustrations

Title page

There should be a separate title page, including the name(s) and address(es) of all author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given and referenced at the appropriate place in the author list by superscript numbers. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spacing should be included.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, methods, results and conclusions, and normally should

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be of 50–150 words. It may be used as it stands by abstracting journals.

Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the international non-proprietary name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

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Discussion

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2 Hull CJ Opioid infusions for the management of postoperative pain In: Smith G, Covino BG, eds *Acute Pain* London· Butterworths, 1985; 155–79

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International Journal of Anaesthesia

Volume 84 Number 6 June 2000

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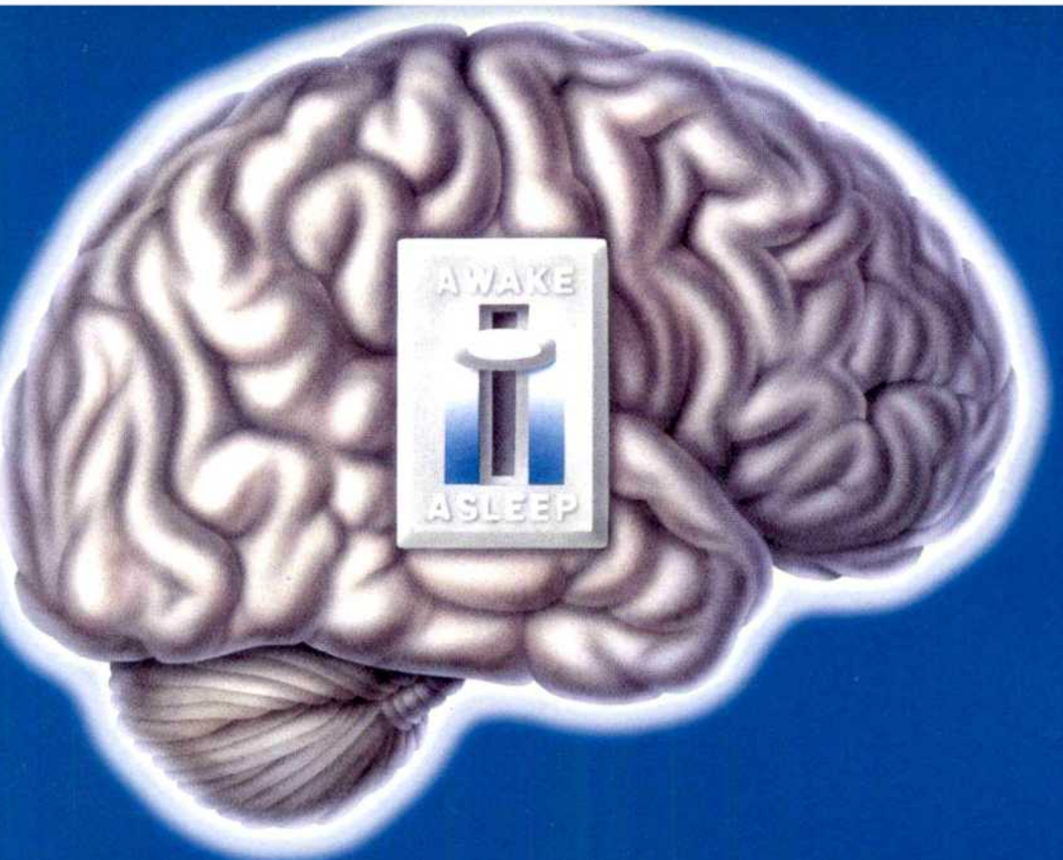

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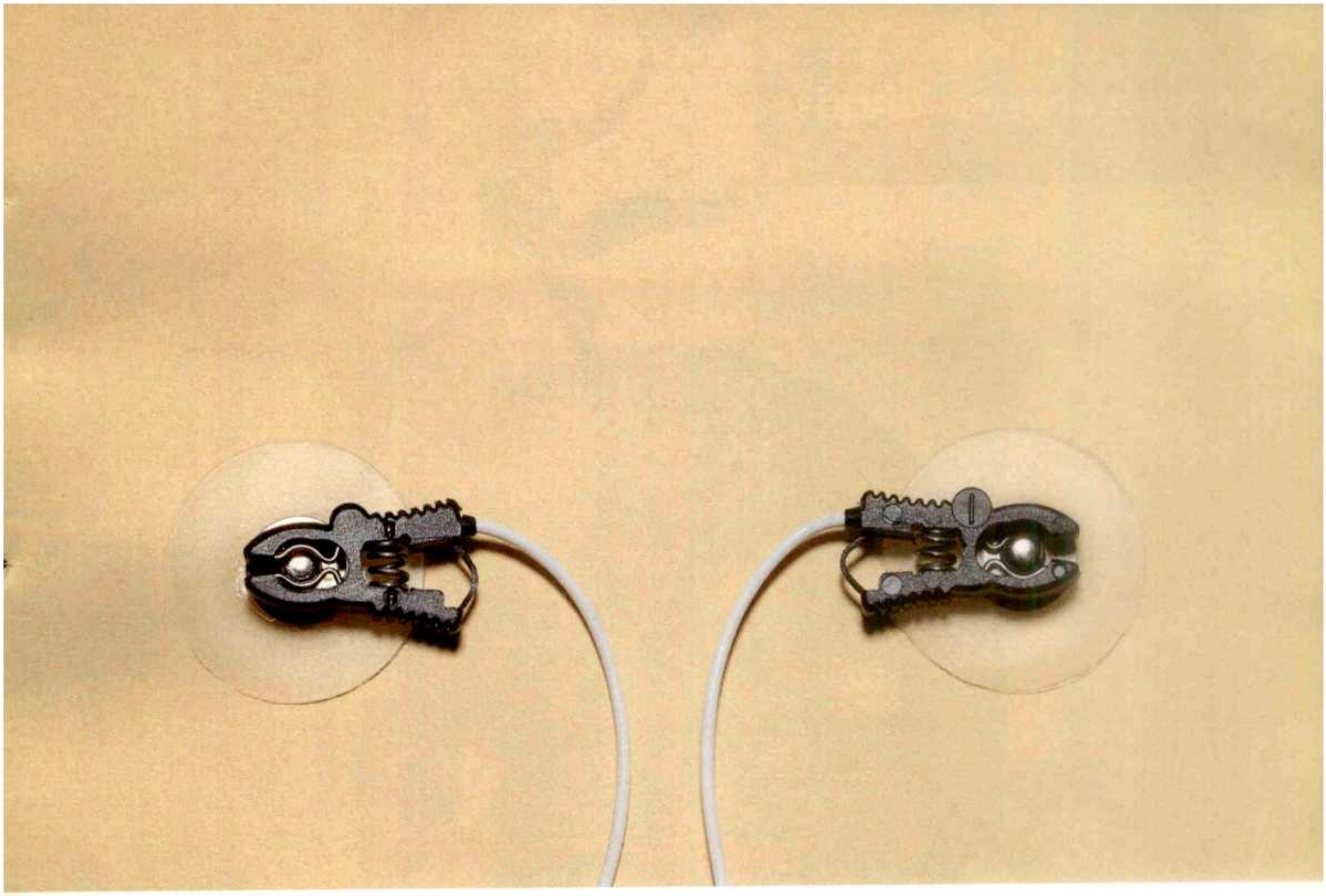

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Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension.

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

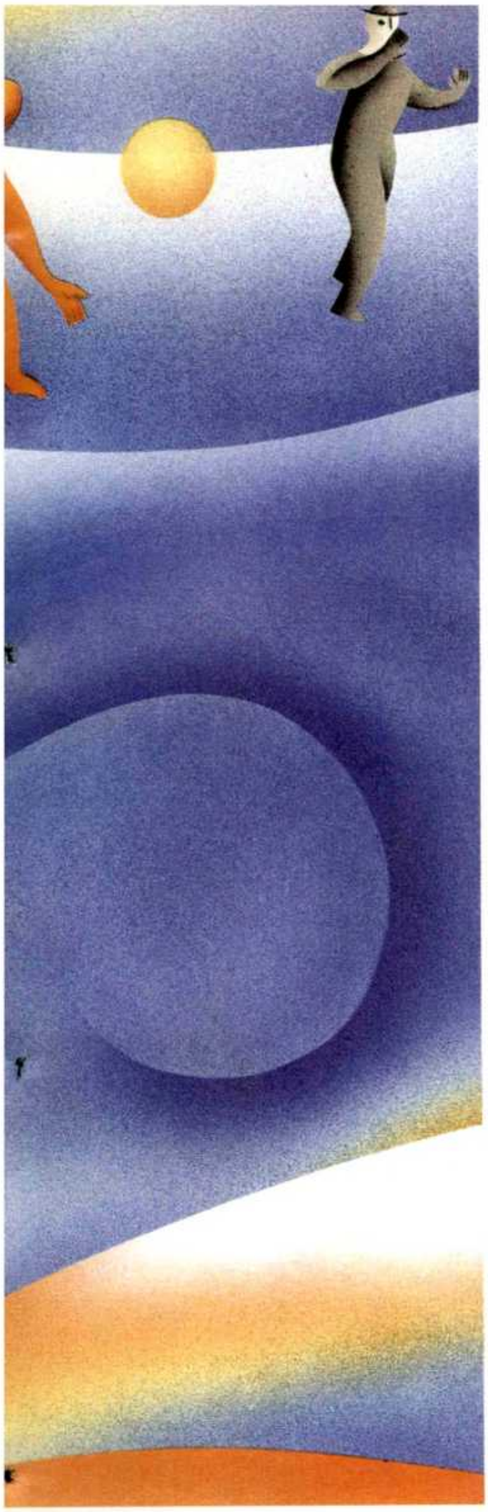
Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib. Rofecoxib may mask fever.

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone.This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of



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rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with rofecoxib for one year or longer.

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

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1. Ehrich EW, Dallob A, De Lepeleire I et al. Characterization of rofecoxib as a cyclo-oxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999; 65(3):336-347.
2. Data on file, Merck Sharp & Dohme Limited.
3. Langman MJ, Jensen DM, Watson DJ et al. Adverse upper gastro-intestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;282(20):1929-1933.

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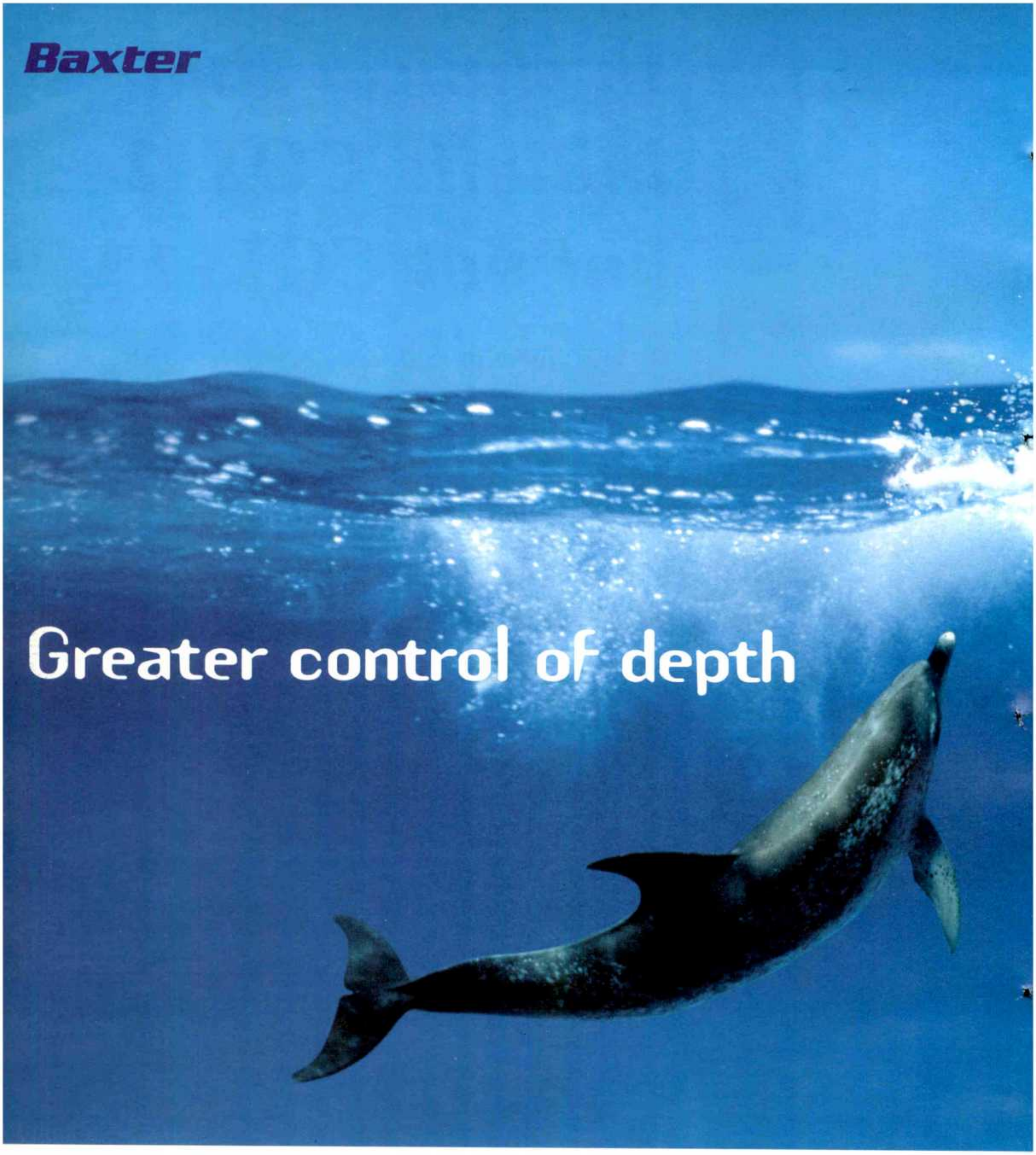
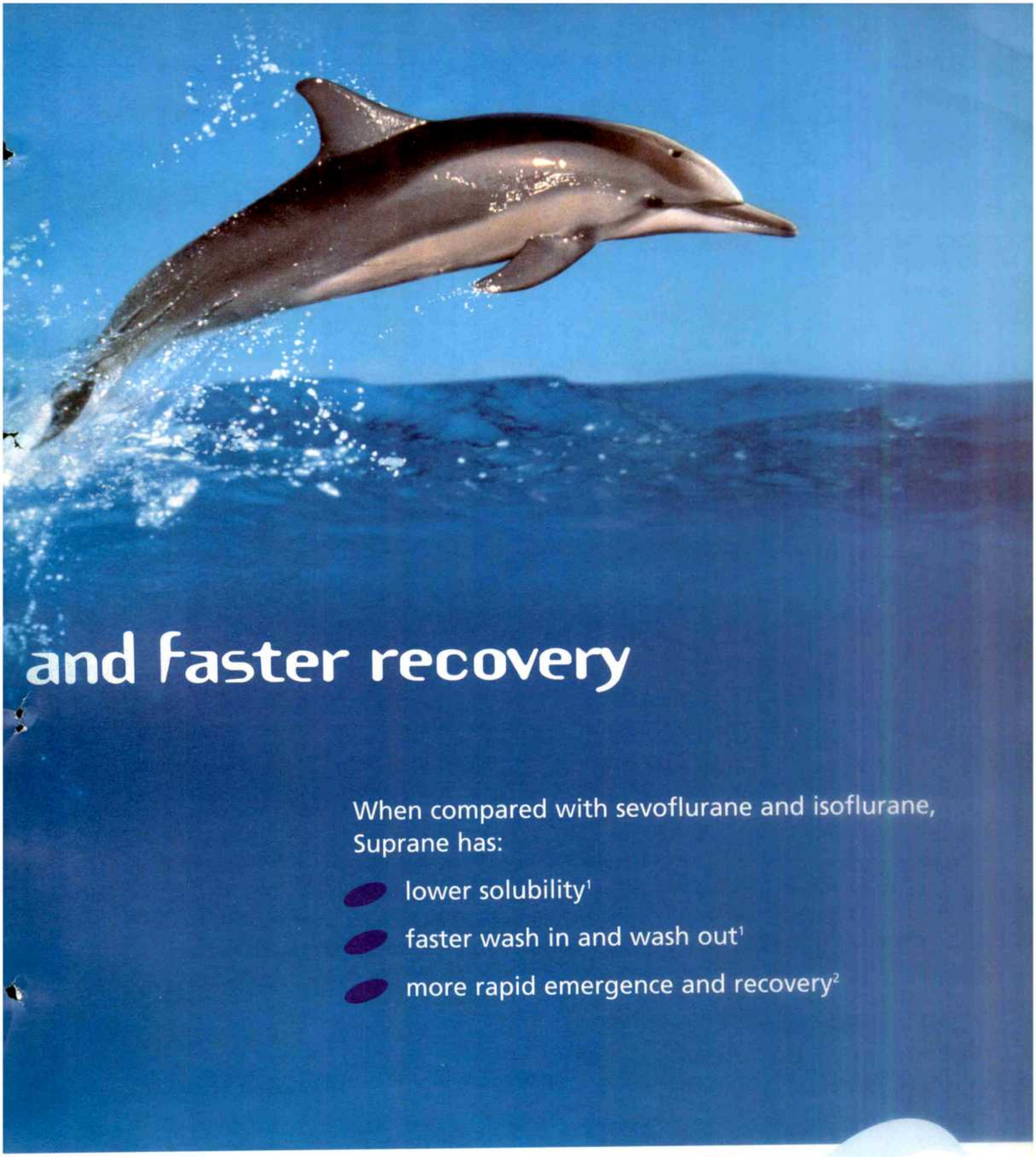


SUPRANE® (desflurane) PRESCRIBING INFORMATION
Presentation: Amber glass bottle containing 240ml desflurane, supplied as pure drug substance. Suprane is a volatile liquid for administration by inhalation. Store in an upright position at room temperature (25°C). **Indication:** Inhalation agent for induction and/or, maintenance of anaesthesia for inpatient and outpatient surgery in adults and maintenance of anaesthesia for inpatient and outpatient paediatric surgery. **Dosage:** Suprane should be administered by trained anaesthetists using a specific vaporiser designed for Suprane. MAC is age-specific and decreases with increasing age. *Induction.* Inspired concentrations of 4-11% of Suprane usually produce surgical anaesthesia in 2-4 minutes. Suprane is not recommended for paediatric induction. *Maintenance.* Surgical anaesthesia may be sustained with 2-6% Suprane when nitrous oxide is used concomitantly. Suprane at 2.5-8.5% may be required when administered using oxygen or oxygen enriched air. Concentrations of up to 18% Suprane have been administered for short periods of time, but if high concentrations are used with nitrous oxide, ensure that the inspired mixture contains a minimum of 25% oxygen. Concentrations of 1-4% in nitrous oxide/oxygen have been used successfully in patients with chronic renal/hepatic impairment. **Contraindications:** Suprane should not be used in patients in whom general anaesthesia is contraindicated, in patients with known hypersensitivity to halogenated agents, or in patients with known or genetic susceptibility to malignant hyperthermia. Suprane should not be used for induction in patients at risk of coronary artery disease or where increases in heart rate or blood pressure are undesirable. **Precautions:** Suprane is not recommended for paediatric induction, or for use in neurosurgical patients. Suprane may increase CSF or intracranial pressure in patients with space occupying lesions. A lower concentration is recommended for hypovolaemic, hypotensive and debilitated patients. Sensitivity hepatitis may be caused in patients previously sensitised by exposure to other halogenated anaesthetics. Suprane has been shown to trigger malignant hyperthermia. To minimise the risk of formation of carbon monoxide in rebreathing circuits, carbon dioxide absorbents should not be allowed to dry out. Suprane is not indicated during pregnancy or breast



and faster recovery

When compared with sevoflurane and isoflurane, Suprane has:

- lower solubility[1]
- faster wash in and wash out[1]
- more rapid emergence and recovery[2]

feeding. **Side effects:** Suprane may cause dose-dependent cardio-respiratory depression. Nausea and vomiting have been observed. Hepatitis may occur in patients sensitised by prior exposure to halogenated anaesthetics. In adult induction, cough, breath holding, laryngospasm, apnoea and salivation have been reported. Transient elevations in white blood cell count have been observed. Rare cases of malignant hyperthermia have been reported. No information exists on the effects of Suprane on the ability to drive or operate machinery. An adequate period, at least 24 hours, is needed to ensure full recovery. **Interactions:** Suprane potentiates commonly used muscle relaxants. Lower doses of Suprane are required in those receiving opioids, benzodiazepines, other sedatives, and nitrous oxide. **Overdose:** There is no experience of overdose in humans. Please consult Summary of Product Characteristics for recommendations in the case of overdosing. **Legal category:** POM. **Packs:** Suprane 240ml in amber glass bottles. **Basic NHS price:** £44.41 per bottle. **PL number:** 0116/0327. **PL holder:** Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk IP24 3SE. **Date of preparation:** December 1999.

® Denotes registered trademark.

References: 1. Eger E I. Anesth. Review. 1993;**20**:87-92. 2. Dupont I et al. Br J Anaesth. 1999;**82**:355-359.

Baxter Healthcare Ltd., Wallingford Road, Compton, Nr. Newbury, Berkshire. RG20 7QW. Tel: 01635 206000

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The University of Pittsburgh Department of Anesthesiology/CCM seeks attending anesthesiologists with fellowship training (or equivalent), for clinical O.R. care of heart/lung transplant recipients in Palermo, Italy. Exciting joint venture of UPMC Health System and the Italian Government. Position involves full time faculty appointment (all ranks) at the University of Pittsburgh, as well as an extremely attractive salary, benefits, and relocation allowance.

Send curriculum vitae and references to:

Leonard Firestone, M.D.
Safar Professor and Chairman
Department of Anesthesiology/CCM
University of Pittsburgh
A-1305 Scaife Hall
Pittsburgh, PA 15261
Fax: (412) 648-1887
E-mail: firestone@anes.upmc.edu

3rd South West Thames Anaesthesia Forum

23-26 October, 2000
(revised dates)
Da Balaia, The Algarve, Portugal

Open to all Anaesthetists - limited to 100 participants

The Scientific Programme will include lectures, and discussions on:

- Acute and Chronic Pain
- Paediatric Update
- Day Case Anaesthesia
- Obstetric Anaesthesia
- Neurology and Anaesthesia
- ITU and Relevant Medical Topics
- Cardiothoracic topics
- Radiology for Anaesthetist
- New Drugs Update
- Training & Education
- Anaesthetic Audit
- Free papers
- Panel Discussions
- Workshops

Guest Speakers
Videos on New Equipment, Drugs and Techniques
Anaesthetists in training presenting papers are eligible for prizes.
Deadline for abstracts: August 13th 2000
This Meeting is approved for CME purposes

For further details, please contact:

Fax: 020 8725 3135
Tel: 020 8725 0018
email: liban@mailbox.co.uk

Dr J.B. Liban
Department of Anaesthesia
St George's Hospital
Blackshaw Road,
London SW17 0QT

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Editorial Notices

5th Congress of the European Resuscitation Council 'Resuscitation 2000'

Antwerp, June 1–3, 2000

Congress Director: Prof. Dr Leo Bossaert

For further information, registration and abstracts, please contact:

ERC secretariat, PO Box 113, 2610 Antwerp, Belgium.

Tel: +32 3 821 36 16; Fax: +32 3 828 48 82; E-mail: erc@uia.ua.ac.be; Website: http://www.erc.edu.

For hotel reservation and tours, contact:

Medicongress, Waalpoel 28/34, 9960 Assenede, Belgium.

Tel: +32 9 344 39 59; Fax: +32 9 344 40 10; E-mail: ERC2000@medicongress.com; Website: http://www.medicongress.com/erc.

*Pre-congress courses in BLS, AED, ALS, PLS on May, 29–31, 2000.

M.E.R.I.T. Centre Bradford Royal Infirmary, Bradford, UK – One day course in Spinal Endoscopy

Bradford, UK, June 9, 2000, September 15, 2000 and October 27, 2000

One day course with lectures, practical equipment demonstrations and observation of the technique in patients. Course material includes a comprehensive, practical guide to all aspects of the technique. Instrumentation is state-of-the-art, and it is anticipated that upon completion delegates will be in a position to consider setting up such a service in their own locality. On-going training will be offered.

Of interest to all those involved in the management and investigation of patients with back pain and sciatica as well as those involved with central neural blocks. Numbers of delegates strictly limited. Lunch will be provided.

For further information please contact:

Dr Jonathan Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford, BD9 6RJ.

Tel: +44 1274 364271/364253; Fax: +44 1274 366811; E-mail: merit.centre@mail.bradh-tr/northy.nhs.uk

Frontiers in Anesthesia

Allergy, Immunology, and Anesthetic Action
Ontario, June 10–12, 2000

The conference will take place at Queen's Landing Hotel, Niagara-on-the-Lake, Ontario, Canada.

For further information and registration, please contact:

Centre for Continuing Education, Tulane University Medical Center, 1430 Tulane Ave, TB 51, New Orleans, LA 70112, USA.

Tel: +1 800 588 5300 or +1 504 588 5466; Fax: +1 504 584 1779; E-mail: cme@mailhost.tcs.tulane.edu.

For further details and electronic registration, visit the web page: http://www.tmc.tulane.edu/anes/niagara/

World Paediatric Anaesthesia Meeting

Nova Scotia, June 14–16, 2000

The meeting will take place at the Westin Nova Scotian Hotel, Halifax, Nova Scotia, Canada.

For further information, please contact:

Dr. John G. Muir, Division of Paediatric Anaesthesia, IWK Grace Health Centre, 5850 University Avenue, Halifax, Nova Scotia, Canada B3J 3G9.

Fax: +902 428 2911. E-mail: wpam2000@is.dal.ca Visit our web site: www.dal.ca/wpam2000.

Therapeutic Applications of Leukocyte Filtration

London, July 7, 2000

The Hammersmith Hospital, Imperial College, London, UK, is pleased to stage a one-day workshop. This prestigious meeting is being organized by Professor Ken Taylor and Dr Terry Gourlay who have invited a guest panel of international speakers.

Topics presented include: Angioplasty Therapy for Acute Myocardial Infarction with Leukocyte Filtration; Filtration of Malignant Cells using Leukocyte Filtration on Cardiopulmonary Bypass; Leucofiltration of Cell Salvaged Blood; Techniques and Timing of Systemic Leukocyte Filtration on Cardiopulmonary Bypass; Leukocyte Depletion in Vascular Surgery; Leukocyte Tactics and Improved Patient Outcome After Extracorporeal Circulation; Leukocyte Filtration in Paediatric Cardiac Surgery; Systemic Leukocyte Filtration during Cardiopulmonary Bypass; Effects of Leukocyte Filtration of Blood Transfusion on Postoperative Complications; The Therapeutic Benefit of Depleting Blood Polymorthonuclear Cells from Patients with SIRS; Role of Leukodepletion in SIRS.

Abstracts are invited for poster presentations at this workshop. Abstract forms are available from the conference centre (address below). Prizes will be awarded to the best three abstracts.

Further details and registration forms are available from:

Jean Bryant, Manager, Wolfson Conference Centre, Imperial College of Science, Technology and Medicine, Hammersmith Hospital, Du Cane Road, London W12 ONN, UK.

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Tel: +44 (0) 208 383 3117; Fax: +44 (0) 208 383 2428; E-mail: wcc@rpms.ac.uk

Edinburgh Anaesthesia Festival

Edinburgh, August, 23–25, 2000

Organized by the Department of Anaesthetics, Royal Infirmary of Edinburgh, to coincide with the 2000 Edinburgh International Festival of the Arts. The 3-day programme consists of lectures and discussion on current topics in anaesthesia. The lecturers are from all parts of the United Kingdom and represent leading opinions in their field.

For further information: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW. Tel: +44 131 536 3652; Fax: +44 131 536 3672; E-mail: anaes@ed.ac.uk

The Fifth Annual Symposium of the Association for Low Flow Anaesthesia

Ulm/Neu-Ulm/Germany, September 8–9, 2000

For further information, please contact:

Priv. Doz. Dr Uwe Schirmer, Priv. Doz. Dr Thomas Marx, Department of Cardiac Anaesthesia, University of Ulm, Steinhövelstr. 9, D-89075 Ulm, Germany.

Tel: +49 731 5021521; Fax: +49 731 5026757; e-mail: alfa2000@gmx.net; congress homepage http://www.uni-ulm.de/alfa2000.

Annual Scientific Meeting in Anaesthesiology 2000

Hong Kong, September 8–10, 2000

We have great pleasure to advise you that the captioned Meeting will be held on 8–10 September 2000 at the Sheraton Hong Kong Hotel and Towers.

Provisional Scientific Programme. Airway Workshop (Prof. David Chung); Regional Anatomy, Workshop for Regional Blocks (Prof. Phillip Bridenbaugh); Evidence Based Medicine Workshop (Dr. Florence Yap and Dr. Gavin Joynt); Keynote Lectures: Perioperative Medicine – International Perspective (Chairman: Dr T. W. Lee) (Prof. Phillip Bridenbaugh); (Prof. Mathieu Gielen); (Dr Neil MacIntyre)

Panel Discussion: Medical Liability *vs* Litigation (Chairman: Dr T. W. Lee) (Mr Douglas Jones and Mr Chris Howse). Debates (Chairman: Dr C. T. Hung) (Prof. Michael Irwin and Prof. Warwick Ngan Kee *vs* Dr Phoebe Mainland and Dr Eddie Cheam); ICU Workshop Weaning from Ventilator (Dr Neil MacIntyre).

Keynote lectures: Perioperative Medicine—International Perspective Chairman: Dr T. W. Lee. The Road Ahead—Anaesthesiologist as Perioperative Physician (Prof. Phillip Bridenbaugh); Lung Protective Ventilatory Strategies (Dr Neil MacIntyre); Perioperative Pain Management—Comfort, Care and Cure (Prof. Mathieu Gielen).

Plenary session I. Test No Test? (Prof. Michael Irwin); Premedication—In or Out (Dr Jeffrey Kua); Perioperative Haemodynamic Goals (Dr Gavin Joynt).

Plenary session II. Preemptive Analgesia: Fact or Fallacy (Prof. Phillip Bridenbaugh); Anaesthetic Techniques—A Look into the Future (Prof Tony Gin); Continuous Spinal Anaesthesia—Is There a Role in Anaesthesia and Postoperative Analgesia (Prof. Mathieu Gielen).

Plenary session III. Chairman: Prof. Tom Buckley. Evaluation and Management of Postoperative Respiratory Insufficiency (Dr Neil MacIntyre); Acid-Base Secrets (Dr Ian Tan); Post-Anaesthetic Care—How Far Should We Go? (Dr C. T. Hung).

Refresher Course topics include: New Analgesic Agents (Dr S. L. Tsui); Anaesthesia for Cerebral Aneurysm Surgery (Dr Sathasivam Anandaciva); Advances in Clinical Measurement (Dr James Derrick); Paediatric Anaesthetic Emergencies (Prof. Cindy Aun); Day Case Anaesthesia (Dr Gwen Fok); Physiology of Consciousness (Prof. Michael Irwin); Spinal Anaesthesia for Day Surgery (Prof. Mathieu Gielen); Clinical Pharmacokinetics (Prof. Tony Gin); Anaesthesia for High-Risk Parturients (Prof. Warwick Ngan Kee); Physiology of Pregnancy (Dr K. K. Lam); Anaesthesia for Thoracic Aneurysms (Dr Das); and TEE (Dr Peter Hiong)

For further information please contact Ms Melissa Leung of the Federation of Medical Societies of Hong Kong. Tel: (852) 2527 8898; Fax: (852) 2866 7530

XIX Annual Congress of the European Society of Regional Anaesthesia Joint Annual Congress with EuroPain 8th European Conference on Pain Research

Rome, Italy, September 20–23, 2000

The congress will be held in the Sheraton Hotel.

Abstract deadline is June 1, 2000.

For further information, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 5643; Fax: +032 2 346 5435;
E-mail: dionne@options.com.cy

Collaborative Conference between Bournemouth University and Salisbury Health Care NHS Trust

Salisbury, UK, September 21, 2000

Day Surgery Conference at Salisbury District Hospital.

For further information please contact: Sam Williams, Administrative Assistant, IHCS, Bournemouth University, Royal London House, Christchurch Road, Bournemouth, BH1 3LT. Tel: +44 (0)1202 504196

Refresher Course in Anaesthesiology

Durban, South Africa, September 22–23, 2000

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–27, 2000

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Surfactant 2000

From Trier to Basle September 23–29, 2000

This is an international floating congress on the rivers Mosel and Rhine. All aspects of surfactant (basic science/clinical applications) will be addressed.

For further information, please contact:

Dr B. Lachmann, Department of Anesthesiology, Erasmus University Rotterdam, Postbox 1738, 3000 DR Rotterdam, The Netherlands.
Web site: http://www.floating-congress.vet.uu.nl

13th Annual Congress of the European Society of Intensive Care Medicine

Rome, Italy, October 1–4, 2000

For further information, please contact:

ESICM Congress Secretariat, 40 Avenue Joseph Wybran, B-1070 Brussels, Belgium.

Tel: + 32 2 559 0355; Fax: +32 2 527 0062; E-mail: public@esicm.org; Internet http://www.esicm.org

Dingle 2000 - Current Controversies in Anaesthesia and Perioperative Medicine

Dingle, County Kerry, Ireland, October 4–8, 2000

University College London Hospitals Centre for Anaesthesia announce a call for abstracts: there is an opportunity to submit work for poster presentation and selected finalists will be invited to give an oral presentation (prizes totalling £1000). Any research is acceptable provided it has not been published in any peer reviewed journal by the abstract deadline of 30 June 2000.

For further abstract and meeting registration details please contact:

Dr Monty Mythen, Centre for Anaesthesia, Room 103, 1st Floor Crosspiece, Middlesex Hospital, Mortimer Street, London, W1N 8AA, UK.

Tel: +44 20 7380 9477; Fax: +44 20 7580 6423;
E-mail: uch.acru@btinternet.com

European Academy of Anaesthesiology European Diploma in Anaesthesiology and Intensive Care

Part I (MCQ), October 7, 2000

(Endorsed by the European Board of Anaesthesiology (EBA) of the Union of European Medical Specialists (UEMS)

This examination will be held in English, French, German, Italian and Spanish in Athens, Barcelona, Berne, Budapest, Cluj-Napoca, Göttingen, Liège, Ljubjlana, London, Lund, Moscow, Oslo, Paris, Poznan, Riga, Rome, Tel Aviv, Uppsala and Vienna.
Regulations and application forms are available from:

Examinations Manager, European Academy of Anaesthesiology, London House, 243 Lower Mortlake Road, Richmond, Surrey TW9 2LS, UK.
Tel: +44 (0)208 940 6240; Fax: +44 (0)208 940 6262; E-mail: DEAA@compuserve.com; Home page: http://eaa-web.eu.org

The closing date for receipt of applications is May 31, 2000 (fee: £170)
Applications received after the closing date or unaccompanied by the full fee cannot be accepted and will be returned.

Wood Library-Museum's Quadrennial Laureate of the History of Anesthesia Prize

Members of the Editorial team of the *BJA* are pleased to announce that, Dr Thomas B. Boulton (UK) and Dr Norman A. Bergman (USA) are to be awarded the Wood Library – Museum's quadrennial Laureate of the History of Anesthesia Prize at the annual meeting of the American Society of Anesthesiologists in October 2000, in San Francisco.

We offer our hearty congratulations to Dr Boulton, and to the family of Dr Bergman, who unfortunately died recently.

Haemostasis and Transfusion—Perioperative Management in Elderly Patients

Graz, Austria, October 27 and 28, 2000

This symposium has been organized by the Department of Anaesthesiology and Intensive Care Medicine, University of Graz and Department of Anaesthesiology, University of Munich.

The preliminary programme includes: haemostasis and transfusion, and perioperative management in elderly patients.

For further information contact: M. Neuray/G. Taucher, Department of Anaesthesiology and Intensive Care Medicine, LKH-Universitätskinikum Graz, Auenbruggerplatz 29, A-8036 Graz, Austria. Tel: +43 316 385 3027; Fax: +43 316 385 4664; E-mail: haemostasis@kfunigraz.ac.at. www.kfunigraz.ac.at/uanwww/haemostasis.htm

St Bartholomew's Hospital Choral Society

Royal Albert Hall, London, UK, November 21, 2000

St Bartholomew's Hospital Choral Society celebrates the millennium and their 35th anniversary with the Royal Medical Benevolent Fund as their chosen Charity for their season 2000/2001.

Mahler's Symphony No. 8 'Symphony of a Thousand' with the Royal Philharmonic Orchestra, Royal Albert Hall, 21 November 2000.

It needs a *really* big choir, splendid orchestra, fine soloists and conductor. Six hundred singers are needed for this monumental work.

To participate contact the Barts Choir Honorary Secretary on:

Tel: +44 1628 664157.

Or to support, details available from:

The Royal Medical Benevolent Fund, 24 King's Road, Wimbledon, London SW19 8QN.

Tel: +44 20 8540 9194; Fax: +44 20 8542 0494;
E-mail: rm.bf@virgin.net

11th Congress, Western Pacific Association of Critical Care Medicine

Singapore November 29–December 3, 2000

This meeting will take place at the Westin Stamford and Westin Plaza, Singapore and is organized by the Society of Intensive Care Medicine (Singapore).

For further information, please contact:

11th WPACCM Congress Secretariat, Academy of Medicine, Singapore College of Medicine, Building 16, College Road, #01-01, Singapore 169854.
Fax: +65 225 5155; E-mail: monicaw@pacific.net.sg

19th Annual Symposium Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

San Juan, Puerto Rico, January 13–20, 2001

Free Papers will be accepted for oral and poster presentation in four categories: (i) monitoring; (ii) new pharmacological agents; (iii) interesting case reports; (iv) cardiopulmonary bypass technology. Abstracts forms are available upon request. The deadline for submission is November 1, 2000. Tuition will not be waived. Brochure available in June 2000.

For information and abstract forms contact: Helen Phillips, Box 1010, Mt. Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029-6574, USA.

Tel: +1 212 241 7630; Fax: +1 212 426 2009; E-mail: helen_phillips@smtplink.mssm.edu

2nd International Conference on Pain Control and Regional Anaesthesia

Jaipur, India, February, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA 4th Workshop 'Neural Blockades on Cadavers'

(European Society of Regional Anaesthesia)

Innsbruk, Austria, February 22–24, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESA 8th Annual Congress

(European Society of Anaesthesiologists)
Gothenburg, Sweden, April 10, 2001

Abstracts deadline: December 1, 2000

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

Anita Akabogy, Congress Department, MCN Medizinische Congress-organisation Nürnberg AG, Zerzabelshofstrasse 29, 90478 Nuernberg, Germany.

Tel: +49 911 393 16 10; Fax: +49 911 393 16 55; E-mail: akabogu@mcn-nuernberg.de; www: http://www.mcn-nuernberg.de

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg, June 13–16, 2001

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

Awareness during Anesthesia—The 2000 *Anesthesiology* Journal-sponsored Symposium at the ASA Meeting

San Francisco, California, October 17, 2000, 9:00–12:30

The moderators will be Alex S. Evers MD (Washington University, St Louis) and Richard B. Weiskopf MD (University of California, San Francisco)

Awareness during anaesthesia is a potential problem of concern to clinicians and the public. There are clear cases of patients having been unintentionally awake during anesthesia and surgery and other cases for which 'awareness' was not as clearly delineated. 'Awareness' during anaesthesia and surgery can result in 'post-traumatic stress syndrome'.

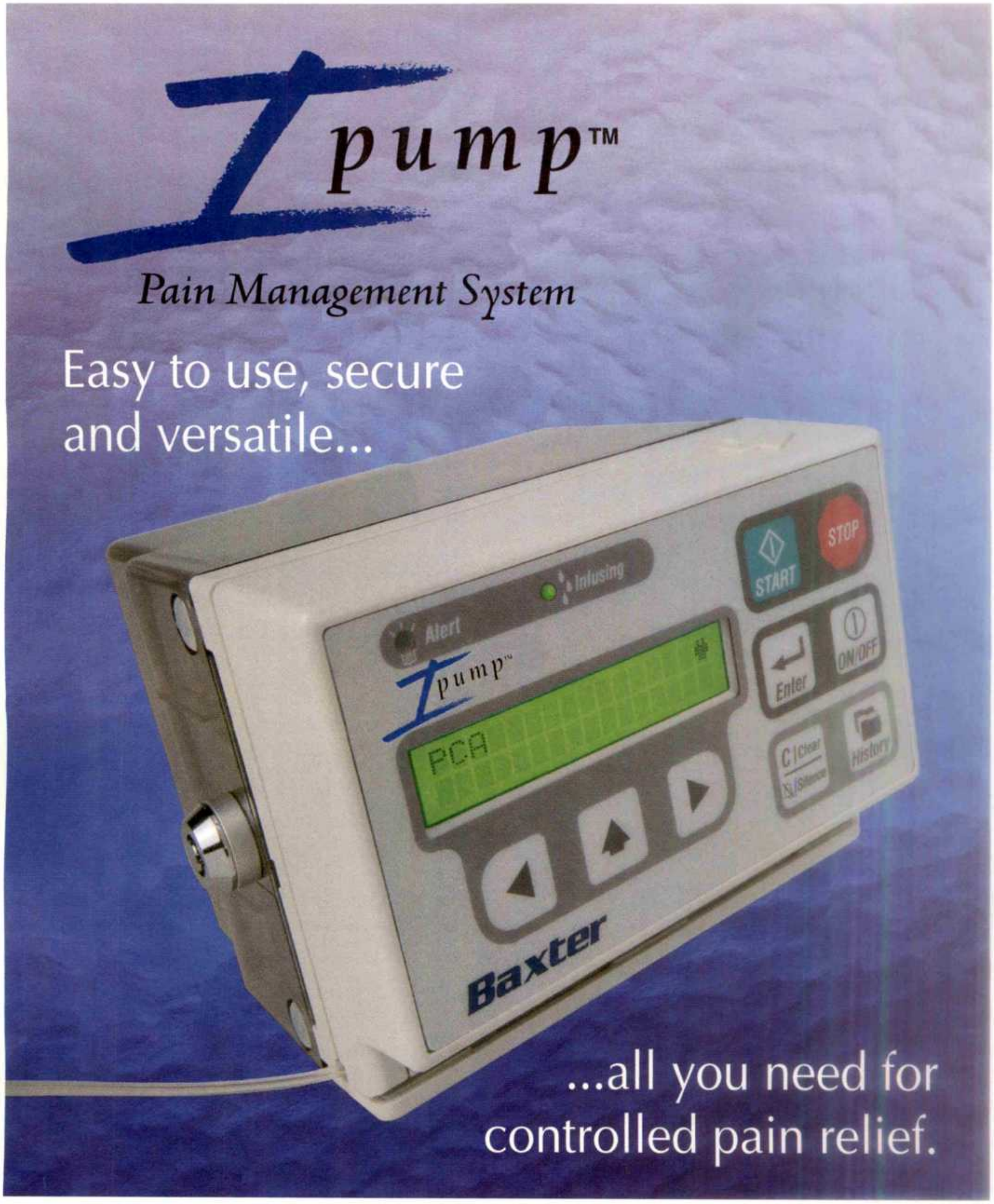
This symposium will include invited speakers and a discussion session, as well as an opportunity to view selected abstracts. Abstracts in the following areas are considered appropriate for submission:

(i) epidemiology of 'awareness' during anaesthesia,
(ii) monitoring of depth of anaesthesia,
(iii) prevention of awareness during anaesthesia,
(iv) treatment of syndromes resulting from awareness during anaesthesia.

Abstracts should be submitted via the regular Annual Meeting procedures by April 1, 2000. *Online submission is available.* Abstracts requesting consideration for presentation at this symposium will undergo an additional review in addition to the standard ASA abstract review process. If you would specifically like your abstract considered for inclusion in the symposium, please check the special box that can be found on the cover letter/form which must accompany your submission. If you need abstract submission materials, please contact the American Society of Anesthesiologists:

American Society of Anesthesiologists, 520 N. Northwest Highway, Park Ridge, IL 60068–2573, USA.

Tel: +1 847 825 5586; Fax: +1 847 825 1692;
E-mail: mail@ASAhq.org Web site: http://www.asahq.org



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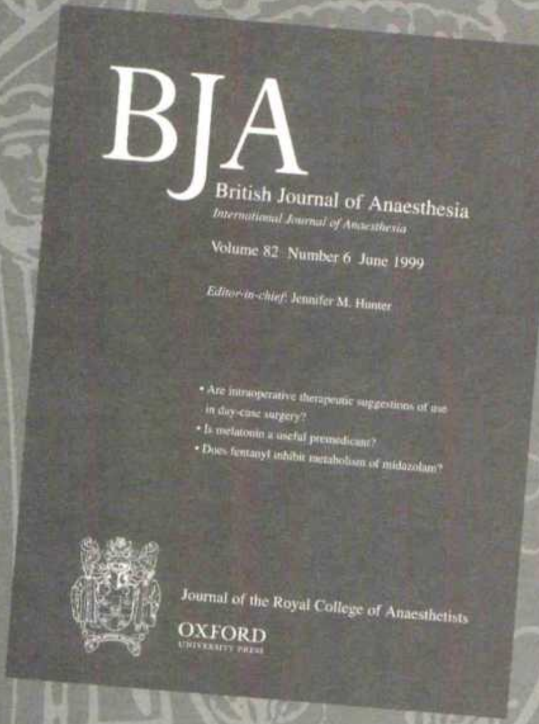

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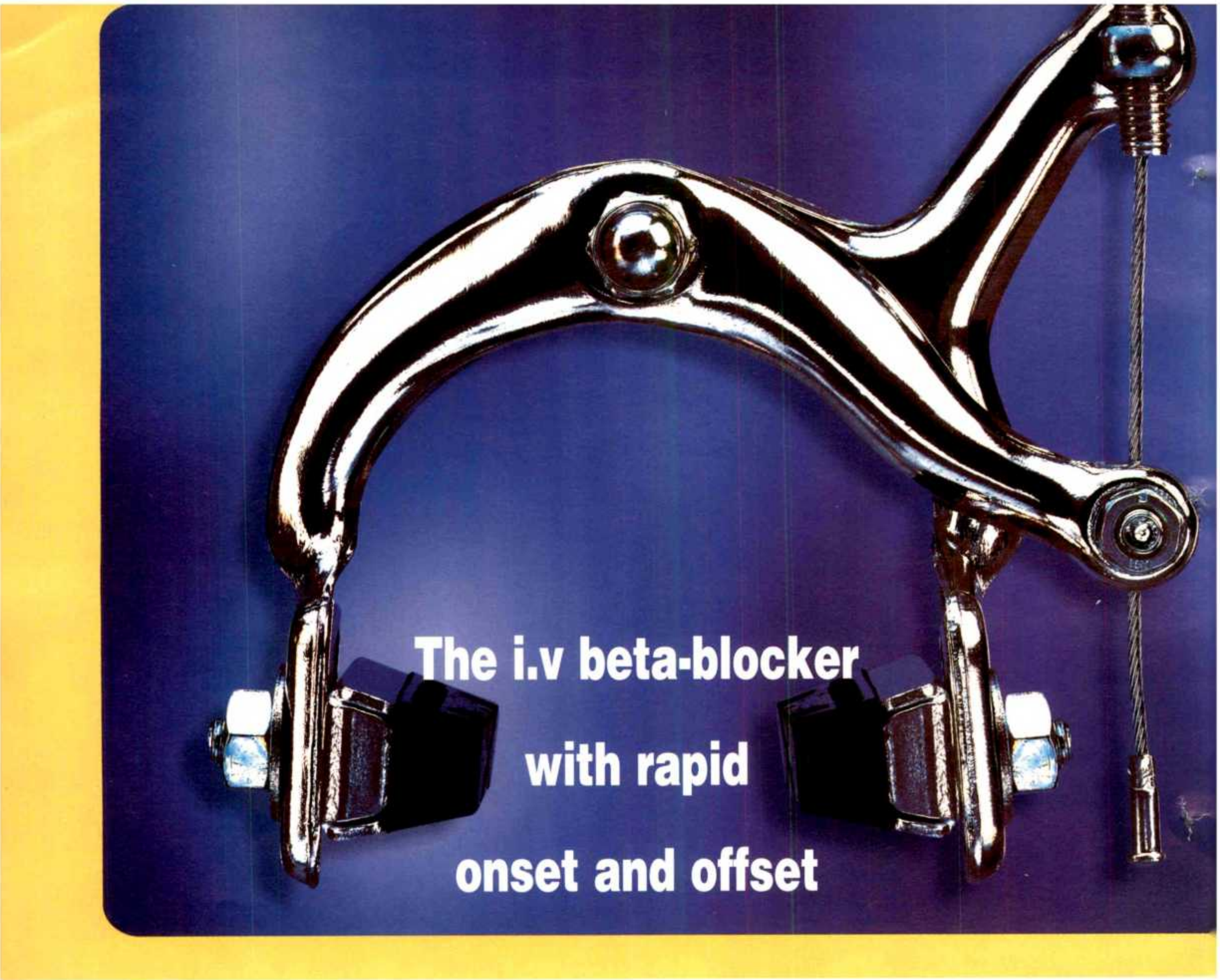

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Editorial I

Spinal cord injury and direct laryngoscopy – the legend lives on

In 1989, Rosen and Wolfe questioned the prevailing dogma that direct laryngoscopy was an unsafe procedure in patients with unstable spines. They suggested that it was in fact a legend, arising mainly from the natural anxieties of physicians.[1] No case reports of spinal cord injury (SCI) at laryngoscopy could be found, nor any evidence to show that the method of intubation made any difference to outcome. In the decade since then, there have been five reports, dealing with nine patients, which allege that SCI resulted from tracheal intubation involving direct laryngoscopy.[2–6] In addition, there has been one report incriminating airway management, when direct laryngoscopy was one of the procedures performed.[7] Is Rosen and Wolfe's 'legend' now fact? Before giving an account of these case reports (where, notably, most of the authors were not anaesthetists), it may be helpful to consider what is currently known about the movements of the cervical vertebrae during intubation, and some experimental and clinical evidence about the induction of a myelopathy.

Most anaesthetists and surgeons probably believe that the risk of SCI during direct laryngoscopy is largely a matter of mechanical compression. Direct laryngoscopy can appear dramatic, even brutal, and it is not surprising that there is concern over the safety of the technique in patients with cervical spine disease, whether the spine is stable or not. The procedure has been accused of causing 'maximal movement and extension of the entire cervical spine' in one of the above reports.[2] However, two studies have concluded that in normal patients and volunteers there is minimal movement below C3 during direct laryngoscopy;[8] [9] this finding is supported by the reduced prevalence of difficult laryngoscopy found in patients with cervical disease below C3.[10] Since cervical movement during laryngoscopy is concentrated at the occipito-atlanto-axial complex, it would seem likely that spinal disease at this level is the most dangerous in terms of the risk of SCI. It can be argued that the amount of movement in the cervical spine from C3 to C7, resulting from laryngoscopy, might be different in unstable spines. It will always be difficult to study the unstable spine, and our knowledge of its movements during intubation (whether the patient is awake or asleep) remains limited. So far, investigations have been confined to cadavers. Donaldson and colleagues studied the movements at the C5–C6 joint before and after surgical destabilization.[11] They found a difference of <2 mm translation and 4° of angulation between the stable and unstable specimens at direct laryngoscopy. Earlier radiographic studies of unstable cervical spines showed that other airway manoeuvres, such as jaw thrust, caused similar degrees of movement.[12] If the deformations of the spinal canal are indeed so small, can an SCI be produced during the few seconds or minutes that is required for direct laryngoscopy?

The development of a myelopathy is believed to result from a combination of mechanical deformation and vascular compromise and, unless the deformation is extreme, the duration of the unfavourable conditions is likely to be a crucial factor.[13] Experimental evidence from animal models of SCI indicates that minor or moderate degrees of compression require some time to produce lasting injury. Dolan, Tator and Endrenyi demonstrated a predictable relationship between the force of cord compression, its duration and the resultant neurological injury.[14] When compression sufficient to produce 50% constriction was applied around dogs' spinal cords, Delamarter, Sherman and Carr found that $\geq$6 h of constriction led to permanent loss of function, whereas after $\leq$1 h of constriction there was nearly complete recovery (although initial neurological impairment was noted in all the dogs).[15] Compression of the cord during laryngoscopy has not been quantified in relation to the movements that occur, although some evidence concerning probable qualitative changes is available. Flexion of the spine causes elongation of the cord with narrowing of the diameter of the longitudinal vessels.[16] Extension causes an increase in diameter of the cervical cord and folding of the ligamentum flavum, which may exert pressure on the cord and the posterior longitudinal vessels.[13] Flow through the radicular vessels is also believed to be obstructed during cervical movement.[13] Dinsmore, Bacon and Hollway have shown that alteration of spinal curvature can increase CSF pressure (and reduce cord perfusion pressure) by 20 mm Hg.[17] All of these effects might be accentuated in the injured or diseased spine. Magnaes, in a remarkable series of investigations on patients with spinal stenosis, showed

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that alteration of head position in simulated laryngoscopy could obstruct CSF flow around the cord.[18] The patients would almost certainly have needed to increase their perfusion pressure to avoid cord ischaemia, but none of them came to harm. It is tempting to suggest that hypertension, which is a notorious feature of direct laryngoscopy, represents a safety factor in patients with cervical spine disease. The contribution of vascular compromise to SCI during anaesthesia has probably been underestimated, while the consequences of spinal movement have been overemphasized. Forty per cent of patients with cervical fractures or dislocations have vertebral artery injuries,[19] and reports of neurological injury induced by cervical manipulation have mostly been of a vascular type of lesion, such as posterior inferior cerebellar artery syndrome.[20]

There is no doubt that hypotension[21] and prolonged malposition can cause cervical cord damage, even in normal patients. Levy reported a case of a man who developed a cervical myelopathy after being tied up in flexion for 12 h.[22] Merli and Staas reported three cases of myelopathy after abnormal body positioning, including one man who spent 8 h sitting with his neck flexed while drunk.[23] Dominguez and colleagues reported the case of a young woman who underwent surgery for the excision of tracheal rings.[24] At the end of the procedure, her chin was stitched to her chest to prevent tension on the tracheal repair. The patient had normal neurology on recovery, but after 8 h she developed an irreversible tetraplegia.

The patients described above suffered neurological damage after major degrees of malpositioning, but there is clear evidence that SCI can occur even when malpositioning is minor. We believe that the case reported by Deem and colleagues[25] is important. They described a man with cervical spondylosis, who required surgery on his lumbar spine. The patient was intubated and then positioned while awake, and normotension was maintained, but at the end of a 6 h procedure the patient was found to have sustained a cervical myelopathy of the central cord type. We have little doubt that, had Deem and colleagues not taken the precaution of intubating the patient awake, the lesion would have been blamed on direct laryngoscopy. Linstedt and colleagues described a 12-yr-old patient, with significant cervical stenosis at the C1 level as a result of mucopolysaccharidosis type IV, who underwent facial surgery for 11 h.[26] The patient was carefully positioned with the head and neck in a neutral position. Three hours into surgery, the cortical sensory evoked potentials (SEPs), which were being used to monitor spinal cord function, suddenly disappeared. The patient's head was slightly anteflexed and the signals returned to normal. Bejjani and colleagues described a patient known to have cervical stenosis and spondylosis, who was undergoing cerebral angiography.[27] The patient's head had been strapped in place, and her complaints that the position was uncomfortable and that her arms were becoming paralysed were treated with diazepam. Cervical myelopathy appears to have started about 45 min after the procedure began. There have been reports of myelopathy occurring in the lumbar and thoracic regions, which have been ascribed to prolonged spinal malposition.[28] A feature common to almost all of these cases is the relatively lengthy period of time that elapsed before the onset of critical spinal cord ischaemia. The immobility induced by general anaesthesia is a highly abnormal condition; it is probably no accident that human beings rarely stay still for long, even in sleep.

Proving that direct laryngoscopy was the cause of an SCI is problematic. Direct laryngoscopy is followed by a period of unconsciousness, during which neurological assessment will be more or less impossible. Alternative possible causes of SCI, such as hypotension and malpositioning, may occur during the period of unconsciousness, but it is also hard to prove that direct laryngoscopy did not cause an SCI. The best we can hope for is likely to be a diagnosis based on a balance of probabilities. We have tried to identify features that would give weight to a diagnosis of direct laryngoscopy-induced SCI. The principal symptoms and signs of acute cervical myelopathy are weakness of the limbs, sensory abnormalities and areflexia; although these will be difficult to assess until the patient is fully conscious, we suggest that these symptoms and signs should be present on recovery. A short period of unconsciousness, which would not allow time for other causes to occur, might also be regarded as evidence that direct laryngoscopy was the cause of SCI. Signs reflecting damage to the autonomic nervous system, such as hypotension, bradycardia and dysrhythmias, which are seen in animal models,[29 30] might be observed after a laryngoscopy that has caused SCI. However, autonomic disturbances are not seen in all myelopathic victims of cervical trauma,[31] so the absence of these signs cannot exclude the diagnosis. The nature of the laryngoscopy must also be considered relevant. It seems probable that an easy laryngoscopy with minimal forces applied, is less dangerous than a difficult one. Disease or instability at the cranio-cervical junction, or gross instability below C3, could also be considered a risk factor. Features tending to add weight to the diagnosis of laryngoscopy-induced SCI could, therefore, include: (i) a myelopathy present on recovery; (ii) a short period of unconsciousness; (iii) autonomic disturbances following laryngoscopy; (iv) difficult laryngoscopy; and (v) cranio-cervical junction disease, or gross instability below C3 (see Table 1). The case reports alleging that SCI resulted from direct laryngoscopy can now be described, and examined for convincing evidence.

Farmer and colleagues[5] reported a series of patients whose neurological condition had deteriorated after an initial injury. They stated that four cases had deteriorated after intubation, but so little information was supplied that it is not possible to assess their report. Farmer and colleagues stated that, in some cases, the patients had deteriorated without any obvious cause. Presumably this phenomenon could coincide with a period of anaesthesia. Redl,[3] Yan and

Table 1 Features given in the text which appear in the referenced case reports (1=myelopathy on recovery; 2=short period of unconsciousness, 3=autonomic disturbances after laryngoscopy, 4=difficult laryngoscopy, 5=cranio-cervical junction disease or gross instability below C3) *Time of onset not given, †cardiac arrest before intubation; NA, not applicable, NR, not reported

Reference	Feature				
	1	2	3	4	5
Farmer and colleagues	NR	NR	NR	NR	NR
Redl[3]	no	no	no	no	yes
Yan and Diggannt[4]	*	no	NR	NR	no
Muckart, Bhagwanjee and van der Merwe[2]	yes	no	no	no	no
Yaszemski and Shepler[6]	NA	NA	†	NR	yes
Hastings and Kelley[7]	yes	yes	yes	yes	no

Diggan[4], and Muckart, Bhagwanjee and van der Merwe[2] stated in the titles of their articles that cord damage was a result of intubation. Redl reported the case of a young man suffering from spondyloepiphyseal dysplasia congenita, who had a severe cranio-cervical abnormality, which was not diagnosed pre-operatively.[3] The patient was intubated easily for an orthopaedic procedure on the lower limbs. The patient had no abnormality on recovery but by the first postoperative day had developed a spastic tetraparesis. The patient described by Yan and Diggan[4] required intubation for AIDS pneumonia, had a normal cervical spine and had neurological abnormalities before intubation. No details of the intubation or intensive care sequence were given, and the patient was found later to have a myelopathy of the central cord syndrome type. An MRI scan was said to show changes consistent with cord contusion, at an unstated level. Muckart, Bhagwanjee and van der Merwe described two patients with undiagnosed cervical fractures, who had surgery for other injuries.[2] The cervical injuries were not discovered pre-operatively, so we presume that no particular attention was given to the alignment of these patient's heads and necks during the operations. Yaszemski and Shepler did not state in the title of their report that direct laryngoscopy had caused an SCI, but in the discussion they did suggest that it had been the cause.[6] Their patient was suffering from rheumatoid arthritis and had reducible atlanto-axial subluxation. A general anaesthetic was administered for hand surgery. Awake fibreoptic intubation was performed and surgery, anaesthesia and recovery were uneventful. Ten hours after the operation, the patient suffered cardiac arrest and had an emergency intubation for cardiopulmonary resuscitation (CPR). Resuscitation was only temporarily successful. A post-mortem examination showed damage to the upper cervical cord and lower medulla. No details of the emergency intubation were provided. Hastings and Kelley[7] were careful not to claim that the cervical myelopathy, which was found to be present after a failed intubation and cricothyrotomy, was a result of direct laryngoscopy. Their patient had developed airway obstruction because of a cervical haematoma, but also had congenital spinal stenosis, osteophytes from C3 to C7, and undiagnosed fractures of the facet joint and lamina of C6–C7. A complex myelopathy was found to be present after resuscitation. The suspicious features in these case reports alleging direct laryngoscopy-induced SCI are summarized in Table 1.

In the case described by Redl,[3] myelopathy was not present until several hours after recovery, so the author's opinion that it was caused by laryngoscopy is difficult to understand. The opinion of Yan and Diggan[4] that the SCI was a result of laryngoscopy seems to have been based on an MRI scan report of 'contusion' of the cord. Our neuroradiological advice is that the MRI signs of contusion are not specific, and the changes could equally have resulted from ischaemia (Stevens JM, personal communication, June 1999). It is not unlikely that the patient had circulatory instability during intensive care admission. The only evidence to support the allegation that cord damage was caused by laryngoscopy in the cases described by Muckart, Bhagwanjee and van der Merwe[2] is that signs of SCI were present when the patients awoke, which is evidence of association rather than causation. It is possible that the alignment of these patients' heads and necks was less than optimal throughout anaesthesia. The case presented by Yaszemski and Shepler[6] is interesting. It is certainly possible that an SCI occurred during direct laryngoscopy, but it is also possible that the damage occurred during CPR, when movement of the head and neck is often quite violent. Sudden death is an uncommon, but well described phenomenon in patients with atlanto-axial instability, so it is also possible that the cord damage was the cause rather than the result of the patient's cardiac arrest and CPR.[32] No sign of a cardiac infarct was found at autopsy. The pathological data presented did not indicate when the cord damage had occurred, beyond saying that the changes must have been *ante mortem*. In the case described by Hastings and Kelley,[7] there are factors other than the immediate presence of myelopathy to support the diagnosis of laryngoscopy-induced cord damage (hypotension at laryngoscopy and difficulty with laryngoscopy). However, the hypotension may already have been present, and the laryngoscopy failed, necessitating a cricothyrotomy, which might have called for extreme neck extension. Nevertheless, Hastings and Kelley's report is the most convincing, although the authors themselves stated that it was not possible to explain the neurological findings in their patient on the basis of laryngoscopy-induced damage alone. It would be foolish to deny the possibility that direct laryngoscopy was the cause of some of the neurological damage, but the severe hypoxaemia, acidosis and hypotension that resulted from the airway obstruction are confounding factors, and the greatest degree of spinal deformation was likely to have occurred during the cricothyrotomy. With the possible exception of Hastings and Kelley's case, the balance of probabilities suggests that direct laryngoscopy was unlikely to have been the cause of the myelopathies reported.

It cannot be denied that SCI caused by intubation may have occurred and yet remained unpublished or simply unrecognized, although it is noteworthy that neither of the UK medical defence organizations has settled a claim for this type of accident. However, we do not seek to downgrade the care which must be taken with direct laryngoscopy in patients with cervical disease. Current recommendations concerning manual stabilization and the use of minimal force at laryngoscopy are *a priori* sensible steps to take. Difficult direct laryngoscopy has a definite associated mortality;[33] flexible fibreoptic technology should be preferred if laryngoscopy is or might be difficult.[10] Pre-operative neurological findings, and any precautions taken should be recorded. A record of adequate care at laryngoscopy could be pertinent to later medico-legal proceedings. More important still is to widen the area of concern to include the whole of anaesthesia and the postoperative period. The overriding aim must be to maintain adequate spinal cord blood flow (SCBF).

The regulation of SCBF is believed to be similar to that of cerebral blood flow. SCBF may become inadequate if arterial pressure is low, because autoregulation of blood flow in damaged cords may be absent.[29] Spinal cord perfusion should be optimized by preventing hypotension, and some workers feel that an element of induced hypertension is beneficial.[34] Conversely, there is also evidence that hypertension may cause increased oedema and haemorrhage in damaged cords,[29] so induced hypertension should be carefully controlled. Perfusion pressure may also be inadequate because the pressure inside the spinal canal or dural sac is high. CSF drainage has been used to promote adequate SCBF in vascular surgery,[35] but its potential benefits in spinal surgery have not been established. Taking care to maintain favourable spinal posture during anaesthesia is clearly important, but it must be admitted that this can be largely guesswork. Deem and colleagues' report[25] demonstrates that even the patient may be wrong about whether a position will be tolerable for an extended period. Monitoring SEP is presently the most practicable way of demonstrating adequate cord perfusion during general anaesthesia. May, Jones and Crockard have used SEP monitoring to identify some risk factors associated with neurological deterioration during surgery on the cervical spine:[36] (i) poor pre-operative neurological function (one third of severely myelopathic patients deteriorated); (ii) use of instrumentation (the risk doubled in pre-operatively unimpaired patients); (iii) upper cervical and clival surgery (the risk tripled); (iv) multisegmental surgery (the risk increased with each additional level). There is, however, no good evidence that monitoring SEP makes any difference to outcome in patients with cervical disease, but the continuing presence of evoked potentials is at least enormously reassuring. It can be argued that the awake patient provides the best monitor of cord function, and the use of local anaesthesia and sedation for cervical surgery may be more practical than is generally supposed,[37] although sedation can make the patient's neurological status difficult to interpret.[38] It is probably true that more use could be made of local anaesthesia and sedation, but successful cervical surgery in awake patients will require considerable commitment from both the surgeon and the patient.

Rosen and Wolfe's legend almost certainly remains a legend, so careful direct laryngoscopy should continue to be an acceptable procedure in patients with unstable cervical spines.[39] However, there can be no doubt that patients with cervical spine disease are at risk of SCI during anaesthesia. Furthermore, it seems that this risk is still present despite ideal anaesthetic care.[5 25] The evidence suggests that spinal cord perfusion can become inadequate during prolonged periods of immobility, probably as a result of minor degrees of malpositioning.[25–27] SEP monitoring of cord function is extremely desirable during high-risk cases, and may help to ensure that the combination of position, blood pressure, cervical pathology, surgery and length of surgery is tolerable.

A. D. M. McLeod
I. Calder
Department of Neuroanaesthesia
The National Hospital for Neurology and Neurosurgery
Queen Square
London WC1N 3BG
UK

References

1 Rosen P, Wolfe RE. Therapeutic legends of emergency medicine. *J Emerg Med* 1989; **7**: 387–9

2 Muckart DJJ, Bhagwanjee S, van der Merwe R. Spinal cord injury as a result of endotracheal intubation in patients with undiagnosed cervical spine fractures. *Anesthesiology* 1997; **87**: 418–20

3 Redl G Massive pyramidal tract signs after endotracheal intubation: a case report of spondyloepiphyseal dysplasia congenita. *Anesthesiology* 1998; **89**: 1262–4

4 Yan K, Diggan MF. A case of central cord syndrome caused by intubation: a case report. *J Spinal Cord Med* 1997; **20**: 230–2

5 Farmer J, Vaccaro A, Albert TJ, Malone S, Balderston RA, Cotler JM. Neurologic deterioration after cervical spinal cord injury. *J Spinal Disord* 1998; **11**: 192–6

6 Yaszemski MJ, Shepler TR. Sudden death from cord compression associated with atlanto-axial instability in rheumatoid arthritis. *Spine* 1990; **15**: 338–41

7 Hastings RH, Kelley SD. Neurologic deterioration associated with airway management in a cervical spine-injured patient. *Anesthesiology* 1993; **78**: 580–3

8 Sawin PD, Todd MM, Traynelis VC *et al.* Cervical spine motion with direct laryngoscopy and orotracheal intubation. *Anesthesiology* 1996; **85**: 26–36

9 Horton WA, Fahy L, Charters P. Disposition of cervical vertebrae, atlanto-axial joint, hyoid and mandible during X-ray laryngoscopy. *Br J Anaesth* 1989; **63**: 435–8

10 Calder I, Calder J, Crockard HA. Difficult direct laryngoscopy in patients with cervical spine disease. *Anaesthesia* 1995; **50**: 756–63

11 Donaldson WF III, Towers JD, Doctor A, Brand A, Donaldson VP. A methodology to evaluate motion of the unstable spine during intubation techniques. *Spine* 1993; **14**: 2020–3

12 Aprahamian C, Thompson BM, Finger WA, Darin JC. Experimental cervical spine injury model: evaluation of airway management and splinting techniques. *Ann Emerg Med* 1984; **13**: 584–7

13 Benner BG. Etiology, pathogenesis, and natural history of discogenic neck pain, radiculopathy, and myelopathy. In: The Cervical Spine Research Society Editorial Committee, eds. *The Cervical Spine*, 3rd edn. Philadelphia. Lippincott–Raven, 1998; 735–40

14 Dolan EJ, Tator CH, Endrenyi L. The value of decompression for acute experimental spinal cord compression injury. *J Neurosurg* 1980; **53**: 749–55

15 Delamarter RB, Sherman J, Carr JB. Pathophysiology of acute spinal cord injury. Recovery after immediate and delayed decompression. *J Bone Joint Surg* 1995; **77A**: 1042–9

16 Breig A, Turnbull I, Hassler O. Effects of mechanical stresses on the spinal cord in cervical spondylosis. A study on fresh cadaver material. *J Neurosurg* 1966; **25**: 45–56

17 Dinsmore J, Bacon RC, Hollway TE. The effect of increasing degrees of spinal flexion on cerebrospinal fluid pressure. *Anaesthesia* 1998; **53**: 431–4

18 Magnaes B. Clinical recording of pressure on the spinal cord and cauda equina. Part 3. Pressure on the cervical cord during endotracheal intubation in patients with cervical spondylosis. *J Neurosurg* 1982; **57**: 64–6

19 Willis BK, Greiner F, Orrison WW, Benzel EC. The incidence of vertebral artery injury after midcervical spine fracture or subluxation. *Neurosurgery* 1994; **34**: 435–41

20 Smith RA, Estridge MN. Neurologic complications of head and neck manipulations. *J Amer Med Assoc* 1962; **182**: 528–31

21 Singh U, Silver JR, Welply NC. Hypotensive infarction of the spinal cord. *Paraplegia* 1994; **32**: 314–22

22 Levy LM. An unusual case of flexion injury of the cervical spine. *Surg Neurol* 1982; **17**: 255–9

23 Merli GJ, Staas WE Jr. Acute transverse myelopathy: association with body position. *Arch Phys Med Rehabil* 1985; **66**: 325–8

24 Dominguez J, Rivas JJ, Lobato RD, Diaz V, Larru E. Irreversible tetraplegia after tracheal resection. *Ann Thorac Surg* 1996; **62**: 278–80

25 Deem S, Shapiro HM, Lawrence F, Marshall LF. Quadriplegia in a patient with cervical spondylosis after thoracolumbar surgery in a patient in the prone position. *Anesthesiology* 1991; **75**: 527–8

26 Linstedt U, Maier C, Joehnk H, Stephani U. Threatening spinal cord compression during anesthesia in a child with mucopolysaccharidosis VI. *Anesthesiology* 1994; **80**: 227–9

27 Bejjani GK, Rizkallah RG, Tzortidis F, Mark AS. Cervical spinal cord injury during cerebral angiography with MRI confirmation: case report. *Neuroradiology* 1998; **40**: 51–3

28 Amoiridis G, Wohrle JC, Langkafel M, Maiwurm D, Przuntek H. Spinal cord infarction after surgery in a patient in the hyperlordotic position. *Anesthesiology* 1996, **84**: 228–30

29 Guha A, Tator CH, Rochon J. Spinal cord blood flow and systemic blood pressure after experimental spinal cord injury in rats. *Stroke* 1989; **20**: 372–7

30 Greenhoot JH, Mauck HP. The effect of cervical cord injury on cardiac rhythm and conduction. *Am Heart J* 1972, **83**: 659–62

31 Zipnick RI, Scalea TM, Trooskin SZ *et al.* Hemodynamic responses to penetrating spinal cord injuries. *J Trauma* 1993; **35**: 578–82

32 Mikulowski P, Wollheim F, Rotmil P, Olsen I. Sudden death in rheumatoid arthritis with atlanto-axial dislocation. *Acta Med Scand* 1975; **198**: 445–51

33 Caplan RA, Posner KL. Medico-legal considerations: the ASA closed claims project. In: Benumof JL, ed. *Airway Management.* New York: Mosby, 1996; 944–55

34 Vale FL, Burns J, Jackson AB, Hadley MN. Combined medical and surgical treatment after acute spinal cord injury: results of a prospective pilot study to assess the merits of aggressive medical resuscitation and blood pressure management. *J Neurosurg* 1997; **87**: 239–46

35 Marini CP, Nathan IM, Efron J, Cohen JR. Effect of nitroglycerin and cerebrospinal fluid drainage on spinal cord perfusion pressure and paraplegia during aortic cross-clamping. *J Surg Res* 1997, **70**: 61–5

36 May DM, Jones SJ, Crockard HA. Somatosensory evoked potential monitoring in cervical surgery. identification of pre- and intraoperative risk factors associated with neurological deterioration. *J Neurosurg* 1996, **85**: 566–73

37 Nygaard ØP, Romner B, Thoner J, Due-Tønnessen B. Local anesthesia in posterior cervical surgery. *Anesthesiology* 1997; **86**: 242–3

38 Miller RA, Crosby G, Sundaram P. Exacerbated spinal neurologic deficit during sedation of a patient with cervical spondylosis. *Anesthesiology* 1987; **67**: 844–6

39 American College of Surgeons Committee on Trauma. *Advanced Trauma Life Support Manual*, 6th edn. Chicago: American College of Surgeons, 1997

Editorial II

The effects of regional analgesia on the progress of labour and delivery

Despite an increasing amount of evidence to the contrary, there is still a widespread belief amongst many healthcare professionals that regional analgesia prolongs labour and increases the number of obstetric interventions. With the introduction of epidural analgesia some 30 years ago came concerns regarding an increased need for instrumental delivery. More recently, the focus of attention has switched to a possible association with Caesarean section, primarily that required for dystocia. Although an association between the use of analgesia and labour outcome exists, a number of recent publications have demonstrated that this relationship is not causative. When examining the effects of regional analgesia on the progress of labour and delivery, study design is crucial, and none of those methods that have been employed is without problems. Retrospective analysis, although frequently cited, is almost worthless, as women do not choose analgesia at random. Consequently, those experiencing prolonged difficult labour, with increased

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risk of intervention, are more likely to request effective analgesia, which only regional block can provide. Moreover, regional block is recommended for those women in whom operative or instrumental delivery is thought to be likely, so that procedures may be performed with adequate pain relief and the hazards of general anaesthesia avoided. Therefore it is to be expected that, with appropriate use of resources, retrospective analysis should indeed find high intervention rates in those women receiving regional analgesia.

Although prospective randomized studies have long been considered the gold standard for scientific research, it is disappointing that so few workers have compared regional with systemic analgesia in labour in this way. In 1993, Thorp and colleagues reported prolonged first and second stages of labour, increased oxytocin requirements and a 12-fold increase in the number of Caesarean sections required for dystocia amongst women randomized to receive epidural analgesia.[1] These findings gained widespread coverage in both the medical and the lay press, although sadly the many criticisms of the study did not. If nothing else, these results encouraged others to conduct randomized studies comparing regional with systemic analgesia, but to date none has managed to reproduce the findings of Thorp's group.[2–6] This inconsistency may result from the major flaw of such randomized work, namely that it is impossible to blind observers to the method of pain relief employed, introducing a potential source of bias.

A meta-analysis[7] based on randomized work found that epidural analgesia was associated with longer first and second stages of labour, although the increases were modest: 42 and 14 min respectively. Instrumental delivery was more common in those receiving epidural analgesia (odds ratio 2.19; 95% confidence interval 1.32–7.78), although Caesarean section was not (odds ratio 1.5; 95% confidence interval 0.81–2.76). The most significant finding of this meta-analysis was the superiority of regional over systemic analgesia. For those of us working in the UK, the fact that all but one of the studies included in this analysis was from North America should not be overlooked. Extrapolation to UK practice may not be entirely appropriate.

In this issue of the *British Journal of Anaesthesia*, Loughnan and colleagues present the results of another large randomized study comparing epidural analgesia with i.m. pethidine.[8] Their finding that the use of regional analgesia was not associated with increases in either instrumental or operative deliveries is reassuring. Although not the first randomized study from the UK, it is arguably the best to date. The authors are to be congratulated for recruiting over 800 nulliparous women into this most difficult of studies. Previous work has been marred by large numbers of women violating the protocol, especially amongst those randomized to receive systemic narcotics. The current study is thus strengthened by the use of intention-to-treat analysis. The uniform management of labour is also to be commended. Other aspects of the study are, however, worthy of comment. All women were offered Entonox and when further analgesia was requested randomization was to either i.m. pethidine or epidural bupivacaine. The implication here is that pethidine is a more potent analgesic than Entonox, although the reverse is probably closer to the truth.[9] The choice of a plain 0.125% bupivacaine epidural infusion was reasonable at the time the study was conducted, although many obstetric anaesthetists would now prefer to use a more dilute solution.[10] Contemporaneous data on the quality of analgesia is not presented, the authors relying on less accurate postnatal assessment. As it appears that the epidural infusions were discontinued at full dilatation, it would have been interesting to record the quality of second-stage analgesia. Assessment of labour and delivery outcomes should not ignore the possible adverse effects on the baby. It is therefore disappointing that only Apgar scores and birth weight are presented. It may be viewed as a missed opportunity that useful data on umbilical cord acid–base status and infant neurobehavioural scoring were not collected.

The potential for observer bias cannot be eliminated in randomized work, and an alternative method of examining the effect of analgesia on labour outcome is by impact studies. Here, the effects of introducing or increasing an epidural service in an individual unit are assessed. Several authors have reported that, despite dramatic increases in the number of women receiving regional analgesia, the number of spontaneous deliveries has not fallen.[11–13] Critics of such methods disapprove of the use of historic controls as this does not take into account changes in clinical practice. However, it may be that such changes are necessary to prevent changes in outcome. Indeed in one centre, the years immediately following an increase in the number of women receiving epidural analgesia saw a rise in the number of instrumental deliveries, only for this figure to return to normal when those managing labour became more familiar with the technique.[11]

Aspects of both obstetric and anaesthetic management need to be addressed when searching for the best way to care for women choosing regional analgesia. Active management of labour, devised in Dublin in the 1960s, comprises antenatal education, strict criteria for diagnosing labour, early amniotomy, psychological support in labour and, where necessary, high-dose oxytocin.[14] Unfortunately, not all studies comparing active with more conventional management have found significant improvements in outcome[15] and none have attempted to randomize epidural with systemic analgesia. The use of oxytocin in the second stage of labour has, however, been demonstrated to improve outcome in nulliparous women receiving epidural analgesia.[16] By blocking sacral afferent pathways, regional analgesia may prevent endogenous oxytocin release. Oxytocin infusion resulted in a shorter second stage and fewer non-rotational forceps deliveries.

Encouraging women to ambulate during labour has been reported by some to shorten labour, reduce analgesia requirements and decrease instrumental delivery. These findings have not been confirmed by all authors, although at the very least mobilizing would appear to do no harm.[17] As with active management, the effects of analgesia have been largely overlooked. This is almost certainly because until recently ambulation has not been encouraged in those receiving regional block. This issue has now been addressed by Collis and colleagues, who randomized 229 nulliparous women receiving combined spinal–epidural analgesia to remain in bed or to mobilize.[18] No differences in the duration of labour or delivery outcome were observed.

Appropriate management of the second stage of labour in women receiving epidural analgesia is vitally important in securing spontaneous delivery. Where regional block is not used, the first sign of the second stage is usually an overwhelming urge to bear down. However, amongst women receiving regional block, full cervical dilatation may be diagnosed on routine vaginal examination, when the fetal head may still be high and there is no desire to push. To start active pushing at this stage increases metabolic disturbance and often leads to maternal exhaustion before spontaneous delivery is achieved. Thus, provided there is no evidence of fetal compromise, a delay in active pushing for 1 h has been shown to increase the chance of spontaneous delivery without adverse effect on the baby.[19 20] With improved fetal monitoring, a more liberal attitude to the duration of pushing has emerged. Provided the mother remains pain-free and well hydrated, the heart-rate pattern of the fetus is reassuring and if there is continued descent, a prolonged second stage is now defined by the American College of Obstetricians and Gynecologists as that greater than 3 h in nullipara and 2 h in multipara. In trying to achieve spontaneous delivery, the risk of maternal neurological, bladder and bowel complications should not be overlooked, although these must be viewed against the adverse effects of instrumentation. Where obstetric intervention is considered, there must be a definite indication. Fetal compromise suggested by a non-reassuring heart trace should be confirmed by blood gas analysis and failure to progress diagnosed only in the presence of adequate contractions.

Although these measures may be viewed as relatively straightforward, it is disappointing that the incidence of obstetric intervention varies widely even within units. In one North American study, the number of Caesarean sections in one unit varied between individual obstetricians, with rates ranging from 9.6 to 31.8%.[21] Similarly, a three-fold increase in the number of Caesarean sections has been found amongst private patients compared with those women managed by obstetric resident staff.[22] These variations existed despite similar rates of regional analgesia.

Although labour management is important, obstetric anaesthetists should not be complacent regarding their own influence on labour outcome. It has frequently been pointed out, although regrettably not often recognized, that regional analgesia is not a generic procedure. Fluid preloading is still widely practised despite evidence that it may temporarily decrease uterine activity.[23] Before siting a block, it makes more sense to assess each woman's fluid needs on an individual basis rather than to routinely infuse a large volume of fluid. Reducing local anaesthetic dose is beneficial in terms of outcome. Fortunately, most obstetric anaesthetists have moved away from repeated boluses of 0.5% bupivacaine, as compared with 0.25%, as its use is associated with profound motor block and increased intervention.[24] The addition of opioids allows further reduction in bupivacaine concentration. Similarly, comparisons of 0.25% bupivacaine with 0.125% or less combined with opioids have shown a reduction in instrumental deliveries.[25 26] However, the use of these dilute solutions may reduce the quality of second-stage analgesia.

New approaches to the management of regional analgesia in labour have been introduced but none has consistently been shown to result in more spontaneous deliveries. Comparisons of intermittent top-ups, infusions and patient-controlled epidural analgesia have found little difference in outcome.[27] Combined spinal–epidural analgesia produces analgesia of rapid onset with little or no demonstrable motor block, but does not appear to increase the number of spontaneous deliveries when compared with more traditional epidural regimens.[28 29]

As with obstetric management, the conduct of regional analgesia during the second stage is vital if intervention is to be avoided. When using intermittent top-ups, allowing analgesia to wear off increases maternal distress without improving outcome, and is therefore to be discouraged.[30] With a continuous infusion the picture is less clear, as providing effective analgesia throughout the second stage may not be possible without increasing the risk of instrumental delivery.[31] However, simply discontinuing an infusion may not be appropriate. When the second stage is diagnosed, the upper and lower limits of the block, the quality of analgesia and the urge to bear down should be checked. If the block extends only to T10 and there is no urge to push, stopping the infusion may result in the return of abdominal pain without the desire to bear down, and is to be avoided. If, however, the block is above T10, a reduction in rate is probably indicated. Should pain develop during the second stage and delivery is not imminent, a top-up should be given and the infusion discontinued.

Although increased intervention is often observed amongst women choosing regional analgesia in labour, this does not imply a cause-and-effect relationship, merely the appropriate use of effective pain relief. Indeed, there is now an increasing number of randomized and impact studies that have failed to demonstrate that regional blocks cause significantly more instrumental and operative deliveries. However, these findings have yet to be universally accepted. Perhaps the time has now come to look at the problem in a different way and to ask why labour is prolonged and spontaneous delivery less likely in some units than in others. The realization that labour with regional analgesia is not the same as that without and that management must be modified will hopefully result in improvements in outcome.

R. Russell
Nuffield Department of Anaesthetics
John Radcliffe Hospital
Oxford OX3 9DU
UK

References

1 Thorp JA, Hu DH, Albin RM, McNitt J, Meyer BA, Cohen GR, Yeast JD. The effect of intrapartum epidural analgesia on nulliparous labor: a randomized controlled prospective trial. *Am J Obstet Gynecol* 1993; **169**: 851–8
2 Ramin SM, Gambling DR, Lucas MJ, Sharma SK, Sidawi JE, Leveno KJ. Randomized trial of epidural versus intravenous analgesia during labor. *Obstet Gynecol* 1995; **86**: 783–9
3 Sharma SK, Sidawi JE, Ramin SM, Lucas MJ, Leveno KJ, Cunningham FG. Cesarean delivery: a randomized trial of epidural versus patient-controlled meperidine analgesia during labor. *Anesthesiology* 1997; **87**: 487–94
4 Gambling DR, Sharma SK, Ramin SM, Lucas MJ, Leveno KJ, Wiley J, Sidawi JE. A randomized study of combined spinal–epidural analgesia versus intravenous meperidine during labor. *Anesthesiology* 1998; **89**: 1336–44
5 Bofill JA, Vincent RD, Ross EL, Martin RW, Norman PF, Werhan CF, Morrison JC. Nulliparous active labor, epidural analgesia and cesarean delivery for dystocia. *Am J Obstet Gynecol* 1997; **177**: 1465–70
6 Clark A, Carr D, Loyd G, Cook V, Spinnato J. The influence of epidural analgesia on cesarean delivery rates: a randomized prospective clinical trial. *Am J Obstet Gynecol* 1998; **179**: 1527–33
7 Halpern SH, Leighton BL, Ohlsson A, Barrett JFR, Rice A. Effect of epidural vs parenteral opioid analgesia on the progress of labor. *JAMA* 1998; **280**: 2105–10
8 Loughnan BA, Carli F, Romney M, Dore CJ, Gordon H. A randomised controlled comparison of epidural bupivacaine versus pethidine for analgesia in labour. *Br J Anaesth* 2000; **84**: 715–9
9 Holdcroft A, Morgan M. An assessment of the analgesic effect in labour of pethidine and 50 per cent nitrous oxide in oxygen (Entonox). *J Obstet Gynaecol Br Commonw* 1974; **81**: 603–7
10 Burnstein R, Buckland R, Pickett JA. A survey of epidural analgesia in the United Kingdom. *Anaesthesia* 1999; **54**: 634–40
11 Bailey PW, Howard FA. Epidural analgesia and forceps delivery: laying a bogey. *Anaesthesia* 1983; **38**: 282–5
12 Fogel ST, Shyken JM, Leighton BL, Mormol JS, Smeltzer JS. Epidural labor analgesia and the incidence of cesarean delivery for dystocia. *Anesth Analg* 1998; **87**: 119–23
13 Impey L, MacQuillan K, Robson M. Epidural analgesia need not increase operative delivery rates. *Am J Obstet Gynecol* 2000; **182**: 358–63
14 O'Driscoll K, Jackson RJ, Gallagher JT. Prevention of prolonged labour. *BMJ* 1969; **2**: 477–80
15 Thornton JG. Active management of labour: does not reduce the rate of caesarean section. *BMJ* 1996; **313**: 378
16 Saunders NJSt, Spiby H, Gilbert L, Fraser RB, Hall JM, Mutton PM, Jackson A, Edmonds DK. Oxytocin infusion during the second stage of labour in nulliparous women using epidural analgesia: a randomised double blind placebo controlled trial. *BMJ* 1989; **299**: 1423–6
17 Lupe PJ, Gross TL. Maternal upright posture and mobility in labour–a review. *Obstet Gynecol* 1986; **67**: 727–34
18 Collis RE, Harding SA, Morgan BM. Effect of maternal ambulation on labour with low-dose combined spinal–epidural analgesia. *Anaesthesia* 1999; **54**: 535–9
19 Maresh M, Choong KH, Beard RW. Delayed pushing with lumbar epidural analgesia in labour. *Br J Obstet Gynaecol* 1983; **90**: 623–7
20 Goodfellow CF, Studd C. The reduction of forceps in primagravidae with epidural analgesia–a controlled trial. *Br J Clin Pract* 1979; **33**· 287–8
21 Goyert GL, Bottoms SF, Treadwell MC, Nehra PC. The physician factor in cesarean birth rates. *N Engl J Med* 1989; **320**: 706–9
22 Neuhoff D, Burke S, Porreco RP. Cesarean birth for failed progress in labor. *Obstet Gynecol* 1989; **73**: 915–20
23 Cheek TG, Samuels P, Miller F, Tobin M, Gutsche BB. Normal saline i.v. fluid load decreases uterine activity in active labour. *Br J Anaesth* 1996; **77**: 632–5
24 Thorburn J, Moir DD. Extradural analgesia: the influence of volume and concentration of bupivacaine on the mode of delivery, analgesic efficacy and motor block. *Br J Anaesth* 1981; **53**: 933–9
25 Olofsson CH, Ekblom A, Ekman-Oreberg G, Irestedt L. Obstetric outcome following epidural analgesia with bupivacaine–adrenaline 0.25% or bupivacaine 0.125% with sufentanil–a prospective randomized controlled study in 1000 parturients. *Acta Anaesthesiol Scand* 1998; **42**: 284–92
26 James KS. McGrady E, Quasim I, Patrick A. Comparison of epidural bolus administration of 0.25% bupivacaine and 0.1% bupivacaine with 0.0002% fentanyl for analgesia during labour. *Br J Anaesth* 1998; **81**: 507–10
27 Purdie J, Reid J, Thorburn J, Asbury AJ. Continuous extradural analgesia: comparison of midwife top-ups, continuous infusions and patient controlled administration. *Br J Anaesth* 1992; **68**: 580–4
28 Collis RE, Davies DWL, Aveling W. Randomised comparison of combined spinal-epidural and standard epidural analgesia in labour. *Lancet* 1995; **345**: 1413–6
29 Price C, Lafreniere L, Brosnan C, Findley I. Regional analgesia in early active labour: combined spinal epidural vs. epidural. *Anaesthesia* 1998; **53**: 951–5
30 Phillips KC, Thomas TA. Second stage of labour with or without extradural analgesia. *Anaesthesia* 1983; **38**: 972–6
31 Chestnut DH. Epidural anesthesia and instrumental vaginal delivery. *Anesthesiology* 1991; **74**: 805–8

Editorial III

Sedation of children by non-anaesthetists

The increasing availability of relatively non-invasive and painless diagnostic procedures such as magnetic resonance imaging (MRI) raises particular problems in paediatric practice. In many institutions manpower restraints prohibit the use of general anaesthesia for all children requiring these procedures. Although older children will often tolerate them without difficulty and some babies will sleep peacefully enough for the procedure to be carried out after a feed, there remains a significant number of children who require sedation if they are to lie quietly enough for satisfactory images to be obtained.

In the 1970s and 1980s it was not uncommon in some institutions for children to be deeply sedated for cardiac catheterization and similar procedures using potent combinations of drugs such as pethidine, promethazine and chlorpromazine. The practice was seldom audited carefully and its safety would nowadays be called into question by many anaesthetists. The difficulty of preventing deep sedation crossing the border into general anaesthesia, with all its consequent risks, has been recognized for several years, as have also the implications of the use of such techniques by non-anaesthetists. In adults, following concerns about sedation in the dental chair, Wylie introduced the concept of 'conscious sedation', in which verbal communication is maintained with the patient whilst sedation is provided using drugs that have a margin of safety which makes unconsciousness with loss of airway reflexes unlikely.[1] The concept of conscious sedation was developed further in 1992 by a Joint Working Party of the Royal College of Anaesthetists and the Royal College of Radiologists. In their report on sedation and anaesthesia in radiology, they reject the concept of the state of deep sedation because of the obvious difficulties of monitoring and preventing the onset of anaesthesia.[2] Unfortunately, this concept of conscious sedation has limited, if any, application in young children, at least during MRI scanning. Undisturbed sleep is required in order to ensure that the child remains quiet and still during the scanning procedure. The American Academy of Pediatrics (AAP) has suggested a defined state of deep sedation as 'a medically controlled state of depressed consciousness or unconsciousness from which the patient is not easily roused. It may be accompanied by a partial or complete loss of protective reflexes and includes the inability to maintain a patent airway independently and respond purposefully to physical stimuli'.[3] Most UK anaesthetists would argue that the only people who could induce and monitor such a state of deep sedation safely are anaesthetists, and many would feel that if anaesthetists are to be present throughout these procedures they are more efficiently employed administering general anaesthesia than supervising deep sedation, which is at best time-consuming and at worst unreliable.

In this issue, Malviya and colleagues present the results of a prospective audit of 922 children receiving sedation for MRI or CT scan compared with 140 children receiving general anaesthesia for these procedures.[4] Their data provide striking evidence both of the potential risks and of the unreliability of their sedation technique. The reported incidence of hypoxaemia, defined as a decrease in oxygen saturation from baseline level by 10% or more for periods in excess of 30 s, is surprisingly high (2.9% in the sedated children), and in a previous publication the same authors report a 20% complication rate, which most of us would find unacceptable.[5] Their 16% incidence of inadequate scans and failed sedation rate of 7% are, however, broadly in line with some other reported series. Failed sedation is particularly distressing, both for the patient's family and for the staff involved, and also has cost implications since the children have to be rescheduled for either repeat sedation or general anaesthesia on a subsequent occasion. Malviya and colleagues conclude that their data support the need for careful selection of appropriate patients for sedation, recognizing that general anaesthesia is a safe alternative in those who fail the selection process. In their study, however, the appropriateness of sedation was reviewed by nurses and radiologists in relation to the child's underlying medical history and physical examination. This suggests that, if they are to improve their results, they need to give further thought to the training of those undertaking the selection process. The fact that sedative agents were ordered at the discretion of the child's primary physician introduces an unquantifiable degree of variability into the process despite the fact that institutional guidelines based on the AAP recommendations were followed.[6]

In our experience of MRI sedation it is necessary to review all aspects of the service if improvements in both safety and reliability are to achieved. This requires the establishment of a multidisciplinary team involving anaesthetists, radiologists, radiographers, paediatricians and nurses. Any review needs to cover not only the selection of patients but also the drugs used and the methods used for drug administration and the monitoring and recovery of the patients. Other fundamental issues include the training and continuing education of staff, regular auditing and the updating of resuscitation skills and the logistics of the whole process. A recently published series from Manchester Children's Hospital showed that significant respiratory depression can occur after oral sedation with chloral hydrate alone if high enough doses are given.[7] Administration of sedation in a ward with the inevitable errors in timing and

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subsequent delays in transport are bound to lead to a higher failure rate than when the drugs are administered within or adjacent to the scan. A review of the roles and responsibilities of all members of the team may enable an extended role to be taken by some staff, such as nurses, whilst reducing or even eliminating the need for immediate anaesthetic supervision. Using this radical approach, it is possible to reduce the failed sedation rate below 5% and to virtually eliminate hypoxaemia and other serious complications. We reported our own results in 1302 children earlier this year;[6] we have now used this approach in over 3000 children without serious complications.

Sedation techniques which work satisfactorily for painless procedures such as MRI are not necessarily applicable to other procedures, especially painful ones such as lumbar puncture or bone marrow aspiration. Although other drugs, such as ketamine, have been used with remarkable safety, most of us would only support the use by non-anaesthetists of drugs with a margin of safety wide enough to render the loss of airway reflexes unlikely.

D. J. Hatch
M. R. J. Sury
Portex Department of Paediatric Anaesthesia
Institute of Child Health
30 Guilford Street
London WC1N 1EH, UK
Department of Anaesthesia
Great Ormond Street Hospital for Children NHS Trust
London WC1N 3JH, UK

References

1 The Wylie Report: Report of the Working Party on Training in Dental Anaesthesia. *Br Dent J* 1981; **151**: 385–8
2 Royal College of Anaesthetists and Royal College of Radiologists. *Sedation and Anaesthesia in Radiology. Report of a Joint Working Party*. London, 1992
3 American Academy of Pediatrics, Committee on Drugs. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. *Pediatrics* 1992; **89**: 1110–15
4 Malviya S, Voepel-Lewis T, Eldevik OP, Rockwell DT, Wong JH, Tait AR. Sedation and general anaesthesia in children undergoing MRI and CT: adverse events and outcomes. *Br J Anaesth* 2000; **84**; 743–8
5 Malviya S, Voepel-Lewis T, Tait AR. Adverse events and risk factors associated with the sedation of children by nonanesthesiologists. *Anesth Analg* 1997; **85**: 1207–13
6 Sury MRJ, Hatch DJ, Deeley T, Dicks-Mireaux C, Chong WK. Development of a nurse-led sedation service for paediatric magnetic resonance imaging. *Lancet* 1999; **353**: 1667–71
7 Keengwe IN, Hegde S, Dearlove O, Wilson B, Yates RW, Sharples A. Structured sedation programme for magnetic resonance imaging examination in children. *Anaesthesia* 1999; **54**: 1069–72

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BJA

CLINICAL INVESTIGATIONS

Randomized controlled comparison of epidural bupivacaine *versus* pethidine for analgesia in labour†

B. A. Loughnan[1]*, F. Carli[2], M. Romney[1], C. J. Doré[3] and H. Gordon[1]

[1]Departments of Anaesthesia and Obstetrics and Gynaecology, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ, UK. [2]Department of Anesthesia, McGill University, 681 Pine Avenue West, Montreal, Canada H3A 1A1. [3]Department of Medical Statistics and Evaluation, Imperial College School of Medicine, Hammersmith Hospital, London, UK

**Corresponding author*

We compared the incidence of Caesarean delivery in nulliparous women randomized to receive epidural analgesia with those randomized to intramuscular (i.m.) pethidine. On admission to the delivery suite in established labour, 802 nulliparae had already agreed to be randomized with respect to their first analgesia. One hundred and eighty-eight women required either no analgesia or 50% nitrous oxide in oxygen (Entonox) only. Of the remaining 614 women, 310 were randomly allocated to receive i.m. pethidine up to 300 mg and 304 to receive epidural bupivacaine. Labour management was standardized according to the criteria for active management of labour. The intention-to-treat analysis showed similar Caesarean section rates in those randomized to epidural (12%) or pethidine analgesia (13%). The difference in Caesarean rate was −1.1% with 95% confidence intervals from −6.3% to +4.1%. The normal vaginal delivery rates were similar (epidural, 59%; pethidine, 61%).

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Epidural analgesia for pain relief in labour is a well-established technique but certain American researchers have suggested a causative link with an increased Caesarean section rate.[1] In a systematic review of all randomized studies published in the previous 25 years, Howell and Chalmers[2] expressed concern that fewer than 600 women had been studied in total. In the majority of studies, not all women randomized were included in the reported results and an intention-to-treat (ITT) analysis was not used. Furthermore, labour was not standardized and the mothers studied were of mixed parity. A more recent meta-analysis by Halpern and colleagues[3] of randomized studies found that epidural analgesia was not associated with an increase in Caesarean section rate.

Our study is a randomized controlled trial of nulliparous women, comparing epidural analgesia with pethidine against the background of labour standardized to the active management protocol.[4–6] In this study we test the hypothesis that epidural analgesia does not in itself increase the Caesarean section rate provided that labour is actively managed and standardized.

Methods

Our maternity unit delivers approximately 3500 women annually and serves a multiracial population with a bias towards social classes 1 and 2. Social class is defined according to the Registrar General's criteria[7] where social class 1 is professional, class 2 is managerial and class 5 is manual unskilled workers. Our bias to social classes 1 and 2 reflects a more affluent population than for the UK overall

The study received Local Research Ethics Committee approval. The research midwife responsible for the study approached all nulliparae with a singleton fetus at 28–30 weeks' gestation, provided written and verbal information about the study and recorded whether the woman would be willing to consider participation. After interview, only those mothers who were not committed to a particular form of analgesia and were happy to be randomized to a type of analgesia were included. At this stage written consent was obtained. We excluded mothers with any factors in their

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obstetric or medical history which would determine the method of analgesia. We only recruited mothers with no systemic disease, an uncomplicated pregnancy with a normal singleton fetus of cephalic presentation and no evidence of cephalopelvic disproportion.

At recruitment, the mother was allocated a study number, and a sealed opaque envelope containing details of her randomized treatment was stapled to her notes. Randomization was generated on an individual basis by computerized random number allocation. The first woman recruited gave birth on December 23, 1992 and the last women recruited gave birth on October 28, 1995.

On admission to the labour ward, all women were assessed and judged to be in labour according to the active management of labour protocol.[4–6] Onset of labour is strictly defined as presence of regular painful uterine contractions together with at least one of; a mucoid or bloody show, cervical dilation of >2 cm, or spontaneous rupture of membranes. Mothers were initially offered Entonox for analgesia; if additional analgesia was requested, and if the woman was still willing to participate in the study, the envelope stating which analgesic was to be administered was opened, and she was given either i.m. pethidine or epidural bupivacaine according to the randomization. Randomization was considered to occur when the envelope stapled to the notes describing the randomized treatment was opened. For ethical reasons, the mothers were told that they could opt out at any stage and only the first type of additional analgesia was randomized.

Mothers randomized to pethidine analgesia could receive up to 300 mg by repeated 100 mg i.m. injections up to every 2 h. Mothers randomized to epidural had a lumbar epidural inserted and an initial dose of 0.25% bupivacaine 10–15 ml was administered to establish adequate analgesia. Thereafter, the women in the epidural group received an infusion of 0.125% bupivacaine at 10–15 ml h^{-1} until the second stage. If required, lidocaine 2% was administered for instrumental or Caesarean delivery.

Labour was managed according to a protocol for active management of labour used on a routine basis by the midwifery staff. This has been in use at our hospital since 1984 and is known to reduce the incidence of labour exceeding 12 h.[8] In the active management of labour, mothers are examined every 2 h and a partogram is plotted; the aim is to produce a rate of cervical dilation of 1 cm h^{-1}. When the rate of dilation falls below this, oxytocin in a concentration of 10 i.u. $litre^{-1}$ is started at a rate of 4 m.u. min^{-1}, increased in 15 min increments to a maximum of 40 m.u. min^{-1} and titrated to allow no more than seven contractions every 15 min. The decision to continue to Caesarean section or other intervention was made by the midwifery and medical staff on the labour ward who were not involved in the study.

Maternal variables recorded included age, final weight, height, marital status and social class (according to the Registrar General's criteria). Obstetric variables included whether labour was induced (with prostaglandin), and whether labour was augmented with oxytocin administration.

Outcomes measured included the duration of the first and second stages of labour, time from first treatment to full dilation and mode of delivery. The duration of epidural analgesia was noted, as was the cervical dilation at the time of analgesia request. Fetal outcomes included infant weight and Apgar score.

Mothers were visited in the maternity ward 24 h after delivery and asked to assess their analgesia in the first and second stages of labour and overall on a five-point scale as excellent, good, satisfactory, poor or very poor.

A prospective sample size calculation was performed. The Caesarean section rates in our hospital in 1988 were 7.8% for women receiving epidural analgesia and 3.8% for those receiving non-epidural analgesia. A total sample size of 1168 women would be sufficient to detect this difference as significant at the 5% significance level with a power of 80%. The original intention of the study was to run over a 3 yr period with recruitment of 1168 patients based on the 1988 Caesarean section figures at Northwick Park Hospital. However, the baseline Caesarean section rate was higher than anticipated (17.9% for epidural patients and 6.7% for non-epidural patients), and there was a clear indication that the analgesia provided in the pethidine arm of the study was inadequate, which led to a higher percentage of protocol violations. A revised power calculation based on these values has shown that two groups each with 271 patients would give the study a power of 90% at a significance level of $P<0.01$.

Statistical analysis was initially performed on an ITT basis to compare the two groups as randomized using Fisher's exact test, chi-squared test, Mann–Whitney *U* test and Student's *t*-test as appropriate. Statistical analysis was performed using Stata v.6 on a PC with a Windows 95 operating system.

Results

Eight hundred and two patients were recruited into the study on going into labour. The outcome of these patients is shown in Figure 1. One hundred and eighty-eight mothers required either no analgesia or required only Entonox and did not proceed to randomization. Of the remaining patients, 304 mothers were randomized to receive an epidural and 310 to receive pethidine. All these 614 patients have been included in the analysis on an ITT basis (Table 1). In both groups there were patients who opted out of their treatment allocation or who required additional analgesia or received Entonox alone.

The two randomized groups were not significantly different in terms of maternal age, weight, height, the proportion of married women and their ethnic group or social class. The proportion of women whose labour was induced was similar in the two groups. There was no significant difference

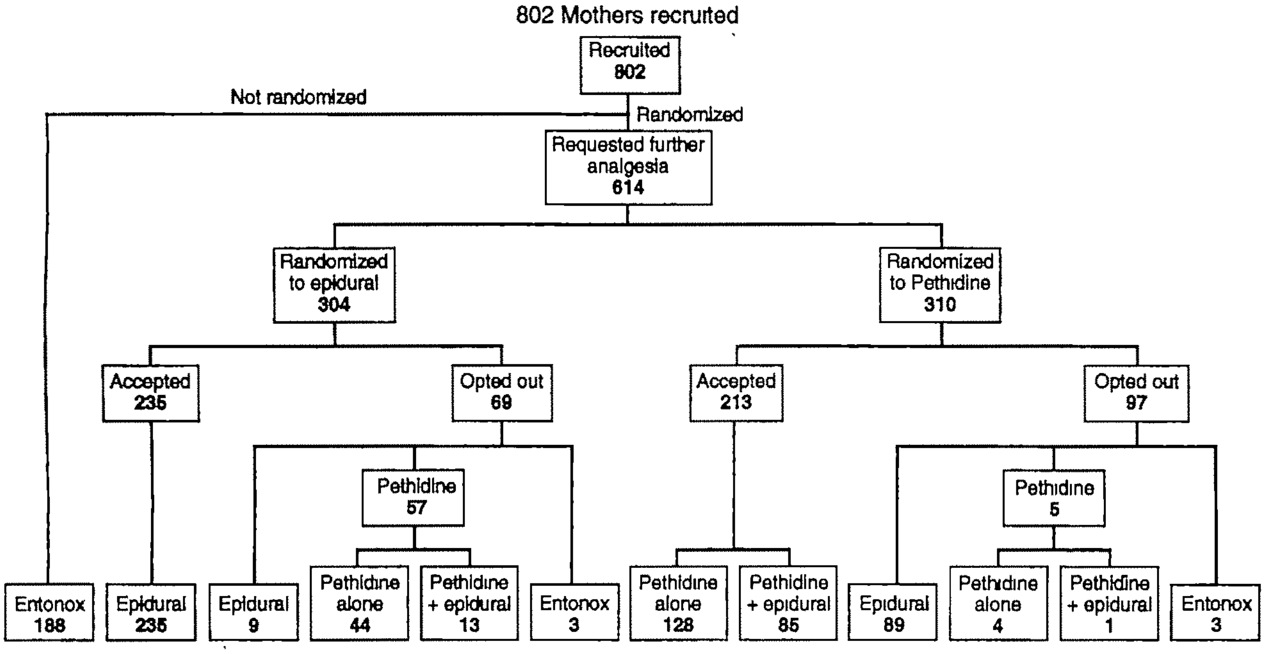

Fig 1 The analgesia outcome for all mothers recruited to the study

Table 1 Intention-to-treat analysis comparing all randomized women Summary statistics are mean (SD or range) for variables analysed by *t*-test, median (interquartile range) for variables analysed by Mann–Whitney *U*-test and frequencies (%) for variables analysed by Fisher's exact test or chi-sqared test

Variable	Epidural ($n=304$)	Pethidine ($n=310$)	*P* value
Treatment received			
Epidural	244 (80%)	89 (29%)	
Pethidine	44 (14%)	132 (43%)	
Pethidine and epidural	13 (4%)	86 (28%)	
Entonox	3 (1%)	3 (1%)	
Age, yr	26.9 (14–42)	26.6 (15–39)	0.4
Final weight, kg	74 (67–84)	75 (67–83)	0.6
Height, cm	162.0 (6.4)	162.6 (6.5)	0.3
Married	212/303 (70%)	207/310 (67%)	0.4
Caucasian	182/302 (60%)	186/307 (61%)	1.0
Social class 1, 2 or 3	213/298 (71%)	235/301 (78%)	0.4
Induced	89/299 (30%)	98/309 (32%)	0.7
Duration of labour, h			
First stage	8.5 (6.3–11.3)	9.0 (6–11.8)	0.8
Second stage	1.3 (0.7–2.2)	1.0 (0.6–2.2)	0.13
Time from first treatment to full dilation, h	3.3 (1.8–5.7)	3.2 (1.6–5.8)	0.5
Duration of epidural, h	5.5 (3.5–8.3)	5.7 (3.4–8.3)	0.8
Entonox	205/304 (67%)	231/308 (75%)	0.04
Oxytocin	186/304 (61%)	175/308 (57%)	0.3
Oxytocin duration, h	2.9 (1.5–5.6)	2.8 (1.4–5.1)	0.5
Mode of delivery			
Normal vaginal	180/304 (59%)	189/310 (61%)	0.9
Instrumental/vaginal	88/304 (29%)	81/310 (26%)	
Caesarean	36/304 (12%)	40/310 (13%)	0.7
Gestational age, weeks	40 (39–41)	40 (39–41)	1.0
Apgar 5 m <9	8/303 (3%)	9/309 (3%)	0.9
Excellent or good pain relief			
In first stage	224/270 (83%)	153/275 (56%)	<0.001
In second stage	215/254 (85%)	149/232 (64%)	<0.001

between the groups in terms of oxytocin augmentation (Table 1).

Women who were randomized to receive an epidural were significantly more likely ($P<0.001$) to grade their pain relief as good or excellent (83% first stage and 85% second stage) compared with those randomized to pethidine (56% first stage and 64% second stage).

The mode of delivery based on the ITT analysis was similar in the two groups (Table 1). The Caesarean section rates were almost identical; there was a slight but insignificant decrease in the normal vaginal delivery rate in the epidural group ($P=0.9$). Overall, 5.4% of mothers had a Caesarean section for fetal distress (5.3% of the epidural group and 5.5% of the pethidine group) and 7% had a Caesarean section for dystocia (6.3% in the epidural group and 7.7% in the pethidine group). There was no difference between the groups. There were 22 admissions to the special care baby unit (12 in the epidural group and 10 in the pethidine group).

Table 2 shows the efficacy of the various regimens based on analgesia received. A total of 226 mothers (48 in the epidural group and 178 in the pethidine group) received one dose of pethidine; 46 (eight in the epidural and 38 in the pethidine group) received two doses and only three (one in the epidural and two in the pethidine group) had three injections of pethidine. Mothers who were in the pethidine group but went on to receive an epidural were more likely to have smaller cervical dilation at first treatment, longer first and second stages of labour and greater oxytocin use. The epidural group showed better pain relief during the first and second stages of labour.

Discussion

We have shown, in a prospective randomized controlled trial in nulliparous women using an ITT analysis, that epidural analgesia does not in itself increase the Caesarean

Table 2 Comparison of women who consented at the start of labour by treatment received Summary statistics are median (interquartile range) or frequencies (%)

Variable	**Pethidine and epidural ($n=99$)**	**Epidural ($n=333$)**	**Pethidine ($n=176$)**
Randomized treatment			
Epidural	13 (13%)	244 (73%)	44 (25%)
Pethidine	86 (87%)	89 (27%)	132 (75%)
Not randomized	0	0	0
Duration of labour, h			
First stage	10.7 (8.6–12.7)	9.2 (7.0–12.3)	6.8 (4.8–9.4)
Second stage	1.7 (0.8–2.5)	1.6 (0.8–2.4)	0.8 (0.5–1.3)
Dilation at first treatment, cm	3 (2–4)	4 (3–5)	5 (4–7)
Time from first treatment to full dilation, h	5.8 (4.0–8.1)	4.0 (2.3–6.2)	1.8 (1.0–3.0)
Induced	30/97 (31%)	108/330 (33%)	47/175 (27%)
Oxytocin	78/99 (79%)	229/333 (69%)	53/174 (30%)
Excellent or good pain relief			
In first stage	35/92 (38%)	253/300 (84%)	86/147 (59%)
In second stage	42/59 (71%)	237/279 (85%)	83/144 (58%)

section rate. This has been observed against a background of labour management that is standardized and actively managed.

Our prospective power calculation was performed on the basis of Caesarean section rates in nulliparae in our unit in 1988: 7.8% if they had epidural analgesia and 3.8% if they had non-epidural analgesia.[9] The greater rates of Caesarean section seen in our study may reflect subsequent changes in practice. Although we had planned to recruit 1168 patients, many women recruited at 30 weeks did not enter the study when in labour. Some mothers opted out later in pregnancy, some delivered elsewhere and some developed 'complications' in the form of clear indications for Caesarean section or epidural analgesia and were therefore excluded.

The major weakness of our study is the number of women who refused their randomized treatment. We had designed this study as a pragmatic clinical trial so that women would only be randomized when they required analgesia. Of the 304 women randomized to epidural, 69 (23%) refused their treatment, whereas the refusal rate for the 310 mothers randomized to pethidine was 97 (31%). This could not be prevented, as an essential ethical requirement for the study allowed the mothers to opt out at any time.

Non-randomized studies[10 11] have shown an association between epidural analgesia and longer labours with an increased rate of instrumental or Caesarean deliveries, but this may not necessarily be causal. Our study confirms the findings of Halpern and colleagues.[3] In their meta-analysis of randomized studies, they found that epidural analgesia was not associated with an increase in Caesarean section rate. The findings of Sharma and colleagues,[12] who used an ITT analysis, are essentially similar to our findings. They also had a high rate of protocol violations, although this was lower than our own. Their lower rate of protocol violations might be accounted for by the fact that they studied multiparae as well as nulliparae. They also used patient-controlled analgesia (PCA) in an attempt to decrease patient crossover. A previous study by the same group[13] had found a high protocol violation rate (only 35% of mothers accepted their randomized treatment) when only bolus i.v. pethidine was used for analgesia, with a higher acceptance of epidural analgesia in nulliparae. Protocol violation was decreased by a superior analgesic regime using PCA in the later study.[12] Use of a PCA regimen might have decreased the rate of protocol violation in this study; however, we wished to use a method in common practice in the UK.

Table 3 Comparison of women in whom the randomized treatment was accepted against those who opted out

Variable	**Opted out of study ($n=166$)**	**Epidural ($n=235$)**	**Pethidine ($n=213$)**
Mode of delivery			
Normal	30%	57%	69%
Assisted	53%	31%	22%
Caesarean section	17%	12%	9%
Excellent or good pain relief			
In first stage	66%	88%	50%
In second stage	70%	88%	61%
Additional analgesia required	8%	0%	40%

Neither of the studies by Sharma and colleagues[12 13] restricted their investigation to nulliparae. This is a particular concern in the latter paper,[13] as the rate of protocol violations was different between nulliparae and multiparae. In our study, we have only investigated nulliparae, as there is much less variability in labour in this group than in multiparae. Current practice is to begin by using a low dose local anaesthetic together with an opiate for analgesia during labour. However, at the time of starting our study, an infusion of 0.125% bupivacaine was standard practice and we had to continue with this regimen for the study period.

Although we cannot draw any firm conclusions based on what the patients actually received, it is appropriate to examine our findings for possible trends to aid further study. Thus, if we compare the epidural group (235 patients) and the pethidine group (213 patients) with those who opted out of their randomized treatment (Fig. 1; $n=166$), we can examine the comparative adequacies of pain relief, the types of delivery and the need for additional analgesia (as extra therapy to their initial choice). This information is presented in Table 3.

Statistical comparison of those patients receiving an epidural ($n=235$) or pethidine ($n=213$) and those either not proceeding to randomization or opting out from their allocated treatment ($n=166$) is not appropriate as it may be subject to considerable bias. There were, nevertheless, differences between groups in the adequacy of analgesia in the first and second stages of labour and in the rates of normal vaginal deliveries and assisted deliveries (Table 3). This would indicate the need for future studies to be based on intention to treat, because of the clear inadequacy of analgesia in all groups other than those receiving epidural analgesia.

This study confirms the findings of other investigators that epidural analgesia is a superior form of analgesia[14 15] and, because of this, mothers are likely to opt for it. Women who request epidural analgesia can be reassured that it is not likely to decrease their opportunity to experience a normal vaginal delivery. Of considerable surprise, however, was the fact that a large number of these nulliparous women (24%) required only Entonox or no analgesia.

In any study of the effect of epidural analgesia on the progress and outcome of labour, the obstetric management must be considered. An active management protocol is associated with a lower rate of Caesarean section for dystocia.[16 17] We follow the guidelines suggested by O'Driscoll and colleagues[8] and have shown in our own population that active management is associated with a lower incidence of Caesarean section in nulliparae.[4 5] The study by Sharma and colleagues[12] used an active management protocol. A lack of clear guidelines to perform Caesarean section may introduce its own bias. However, the large numbers studied should help to obviate this.

In summary, we have shown that, in a standardized actively managed labour, there is no increased incidence of Caesarean section associated with epidural analgesia.

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References

1 Thorp JA, Hu DH, Albin RM, McNitt J, Meyer BA, Cohen GR, Yeast JD. The effect of intrapartum epidural analgesia on nulliparous labor; a randomized, controlled prospective trial. *Am J Obstet Gynecol* 1993; **169**: 851–8

2 Howell CJ, Chalmers I. A review of prospectively controlled comparisons of epidural with non-epidural forms of pain relief in labour. *Int J Obstet Anesth* 1993; **2**: 15–20

3 Halpern SH, Leighton BL, Ohlsson A, Barrett JFR, Rice A. Effect of epidural vs parenteral opioid analgesia on the progress of labor. *JAMA* 1998; **280**: 2105–10

4 Turner MJ, Webb JB, Gordon H. Active management of labour in primigravidae. *J Obstet Gynaecol* 1986; **7**: 79–83

5 Turner MJ, Brassil M, Gordon H. Active management of labor associated with a decrease in the cesarean section rate in nulliparas. *Obstet Gynecol* 1988; **71**: 150–4.

6 Glantz JC, McNanley TJ. Active management of labour; a meta-analysis of Cesarean delivery rates for dystocia in nulliparas. *Obstet Gynaecol Surv* 1997; **52**: 487–501

7 Office of Population Census and Surveys. *Standard Occupational Classification*, Vol. 3. London: HMSO, 1991

8 O'Driscoll K, Foley M, MacDonald D. Active management of labor as an alternative to cesarean section for dystocia. *Obstet Gynecol* 1984; **63**: 485–90

9 Carli F, Creagh-Barry P, Gordon H, Logue MM, Dore C. Does epidural analgesia influence the mode of delivery in primiparae managed actively? A preliminary study of 1250 women. *Int J Obstet Anesth* 1993; **2**: 15–20

10 Thorp JA, Eckert LO, Ang MS, Johnston DA, Peaceman AM, Parisi VM. Epidural analgesia and cesarean section for dystocia; risk factors in nulliparae. *Am J Perinatol* 1991; **8**: 402–10

11 Studd JW, Crawford JS, Duignan NM, Rowbotham CJ, Hughes AO. The effect of lumbar epidural analgesia on the rate of cervical dilatation and the outcome of labour of spontaneous onset. *Br J Obstet Gynaecol* 1980; **87**: 1015–21

12 Sharma SK, Sidawi JE, Ramin SM, Lucas MJ, Leveno KJ, Cunningham FG. A randomized trial of epidural versus patient-controlled meperidine analgesia during labor. *Anesthesiology* 1997; **87**: 487–94

13 Ramin SM, Gambling DR, Lucas MJ, Sharma SK, Sidawi JE, Leveno KJ Randomized trial of epidural versus intravenous analgesia during labor. *Obstet Gynecol* 1995; **86**: 783–9

14 Robinson JO, Rosen M, Evans JM, Revill SI, David H, Rees GA. Maternal opinion about analgesia for labour. A controlled trial between epidural block and intramuscular pethidine combined with inhalation. *Anaesthesia* 1980; **35**: 1173–81

15 Philipsen T, Jensen NH. Maternal opinion about analgesia in labour and delivery. A comparison of epidural blockade and intramuscular pethidine. *Eur J Obstet Gynecol Reprod Biol* 1990; **34**: 205–10

16 Peaceman AM, Socol ML. Active management of labor. *Am J Obstet Gynecol* 1996; **175**: 363–8

17 Lopez-Zeno JA, Peaceman AM, Adashek JA, Socol ML. A controlled trial of a program for the active management of labor. *New Engl J Med* 1992; **326**: 450–4

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Epidural ropivacaine with fentanyl following major gynaecological surgery: the effect of volume and concentration on pain relief and motor impairment

R. Whiteside[1 2*], D. Jones[1 3], S. Bignell[4 5], C. Lang[1 6] and S. K. Lo[7]

[1]*Division of Anaesthesiology and Intensive Care, Royal Brisbane Hospital, Brisbane, 4029, Queensland, Australia*
Present addresses: [2]*Ipswich Hospital, Ipswich 4305, Queensland, Australia.* [3]*Tsim Sha Tsui East, Hong Kong.* [4]*Department of Anaesthetics, Royal Women's Hospital, Brisbane, 4029, Queensland, Australia.* [5]*Division of Anaesthesiology and Intensive Care, Royal Brisbane Hospital, Brisbane, 4029, Queensland, Australia.* [6]*Stirling Royal Infirmary, Livilands, Stirling, Scotland.* [7]*Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong*

**Corresponding author: Ipswich Hospital, Ipswich 4305, Queensland, Australia*

In a prospective, randomized, double-blind study, 40 patients undergoing gynaecological oncology surgery received either 0.1% ropivacaine with fentanyl 1 μg ml^{-1} or 0.2% ropivacaine with fentanyl 2 μg ml^{-1}. A PCEA pump was set to deliver ropivacaine 8 mg with fentanyl 8 μg with each successful demand and a lockout period of 15 min without background infusion. Patients were observed for rest and activity pain VAS, side effect incidence, peak expiratory flow rate (PEFR), leg strength, sensory block to cold and pinprick, and PCEA usage into the second postoperative day. Passive and active pain scores for both groups were both satisfactory and comparable for the duration of the study. There were no differences between groups with regard to side effects. There was a 24% increase in total drug used in the high-concentration/low-volume group ($P<0.05$). The study demonstrated that PCEA ropivacaine with fentanyl is an effective means of postoperative analgesia for this patient population. Reduced drug consumption with high-volume/low-concentration solution confirms similar findings by other investigators using alternate local anaesthetic agents, and suggests that the therapeutic ratio of ropivacaine is widened if a low-concentration/high-volume solution is used.

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A combination of local anaesthetic with opioid by infusion into the epidural space provides effective postoperative analgesia for patients undergoing major abdominal gynaecological surgery, but not without risk of potentially lethal effects.[1] Ropivacaine is a local anaesthetic with an epidural potency similar to bupivacaine[2] which displays an improved cardiotoxicity profile[3] and reduced motor block at doses which provide analgesia.[4] Without addition of opioid, epidural 0.2% ropivacaine by infusion is considered the most effective concentration for postoperative analgesia.[5] There is some evidence that a high-volume/low-concentration epidural (HVLC) solution is as effective as a low-volume/high-concentration (LVHC) solution for relieving pain with less drug needed overall.[6] If this were so, then administration of HVLC ropivacaine for epidural analgesia should provide an even greater margin of patient safety and also allow early mobilization with maintenance of pulmonary function. Patient-controlled epidural analgesia (PCEA) allows the patient to relieve their postoperative pain[7] without interference by a subjective assessor. If analgesia is self-administered to provide comfort, then any difference in total dose should be due to the composition of the analgesic solution.

In a randomized, prospective, double blind manner, we compared the effects of concentration and volume on a ropivacaine–fentanyl mixture given epidurally for postoperative analgesia in women who had undergone gynaecological oncology laparotomy.

Material and methods

Forty, ASA II–III women (20–79 yr, 40–120 kg) undergoing laparotomy with a combined general–epidural anaesthetic technique for ovarian, uterine or cervical cancer were

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enrolled prospectively over a period of 1 yr to participate in a study approved by the Royal Women's Hospital Ethics Committee. Each patient received a verbal and written description of the research protocol and all gave written consent. Exclusion criteria included inability to use PCEA, chronic pain, NSAID administration or drug abuse, and allergy to local anaesthetic or fentanyl.

Preoperative and intraoperative care followed a standard regimen. Patients were premedicated with oral temazepam 10–20 mg and metoclopramide 10 mg 1 h preoperatively. During surgery, the patient was monitored using the Datex AS3 system (Datex Instrumentarium, Helsinki, Finland). Direct arterial pressure, electrocardiograph and pulse oximetry monitoring were established before induction of anaesthesia. Fentanyl 1 μg kg^{-1} and midazolam 0.02 mg kg^{-1} were given i.v. 60 s prior to the commencement of induction of anaesthesia with propofol 2 mg kg^{-1}. Vecuronium 0.1 mg kg^{-1} was administered to facilitate tracheal intubation and mechanical ventilation. Patients were ventilated to obtain an end-tidal carbon dioxide concentration of 4.6 kPa and anaesthesia was maintained with 1% isoflurane in nitrous oxide and 35% oxygen. The patient was turned to the left lateral position and an epidural catheter placed via an 18-gauge Tuohy needle at a thoracic interspace ($T_{9/10}$, $T_{10/11}$ or $T_{11/12}$ depending upon the proposed surgical incision) and advanced 5 cm inside the epidural space. Two 5-ml boluses of an epidural solution containing 0.2% ropivacaine with fentanyl 2 μg ml^{-1} were administered over 2 min, 5 min apart, followed by a continuous infusion of the same solution at 8 ml h^{-1} (IMED Gemini PC-1, San Diego, CA, USA). A further bolus of 5 ml epidural solution was administered if haemodynamic data increased 20% above the baseline, and increments of i.v. fentanyl and vecuronium were given as indicated. Crystalloid and colloid were administered together with 3-mg boluses of ephedrine to maintain mean arterial pressure within 20% of baseline values, and packed cells were given intraoperatively when blood loss exceeded 10% of estimated blood volume (70 ml kg^{-1}). At the end of the operative procedure, muscle relaxation was reversed with neostigmine and atropine.

In the recovery room, the epidural infusion was ceased and a PCEA device (Abbott Pain Management Provider Pump, Abbott Laboratories, North Chicago, IL, USA), programmed and primed with the trial solution by an independent anaesthetist, was attached to the patient and education in the use of the device was reinforced. All patients were block randomized to receive, in a double blinded manner, either 0.1% ropivacaine with fentanyl 1 μg ml^{-1} (HVLC) or 0.2% ropivacaine with fentanyl 2 μg ml^{-1} (LVHC) prepared by the Royal Brisbane Hospital Central Pharmacy. The PCEA was programmed to deliver a bolus dose of ropivacaine 8 mg with fentanyl 8 μg (HVLC group received an 8-ml bolus on successful demand and the LVHC group a 4-ml bolus), with a 15-min lockout period and without any background infusion.

Table 1

Visual analogue score (VAS)	
Commencing at 50 mm. Scale 0–100 mm	
0=no pain, , 100=worst pain ever experienced	
Modified Oxford score (at the hip)	
0	no muscle contraction
1	hip flexors/extensors contract but thigh does not move
2	able to lift thigh or move against gravity but not against resistance
3	able to lift thigh against resistance but readily overcome
4	full range of movement against gravity and able to withstand maximal resistance
Sedation score	
1	awake, alert, cooperative, able to complete VAS
2	awake but appears sleepy, cooperative, able to complete VAS
3	sleeping but easily aroused, or awake but unable to complete VAS
4	sleeping, difficult to rouse
5	unresponsive to painful stimulus
Nausea/vomiting score	
1	no nausea or vomiting
2	nausea but no vomiting, no treatment requested
3	nausea but no vomiting, treatment requested
4	vomiting
5	vomiting which persists after treatment
Pruritus score	
1	none
2	mild, present but not distressing
3	moderately distressing, but treatment not required
4	severe; treatment requested
5	poor relief with treatment

The pump and nursing chart displayed the dose of drug in milligrams delivered. Data were collected at 1, 4 and 8 h after discharge from the recovery room, and then at 08:00, 12:00, 16:00 and 20:00 h on postoperative days 1 and 2. Analgesia was assessed using a 10-cm visual analogue scale (VAS) at rest (passive pain score) and during performance of peak expiratory flow rate with the patient semi-reclined, and leg raising with patient flat (active pain score). Sensory block to cold and pin prick was assessed together with muscle power (modified Oxford motor power score[8]). The incidence and severity of unwanted effects such as hypotension, nausea/vomiting, sedation and pruritus were also assessed (Table 1). PCEA data such as the number of boluses and attempts and total dose were downloaded directly via the RS232 serial port of the Abbott pump to a laptop computer at the completion of each study.

A preliminary estimate of sample size was based on an expected 25% difference in dose requirements between the HVLC and LVHC groups. With a type I error of 0.05 and a type II error of 0.2, the required sample size was 40 patients (Power Analysis & Sample Size for Windows PASS v.6.0, NCSS, Kaysville, UT, USA). Data were collated using Excel 95 and statistical analysis performed using Arcus Quickstat (Biomedical) version 1.2 (Addison Wesley Longman, Cambridge 1998). Nominal data were analysed by unpaired *t*-test while VAS data were analysed by Mann–Whitney *U*-testing. A value of $P<0.05$ was considered significant.

Table 2 Patient characteristics Data are mean (SD or range) or number. Peak expiratory flow rate data [mean percentage decrease in PEFR from baseline (SD)]

	HVLC	LVHC
Age (yr)	52.6 (26–65)	51.8 (33–68)
Height (cm)	161 (5 2)	164 (7.1)
Weight (kg)	71.6 (17.6)	68.2 (13)
ASA class (II/ III)	13/5	16/2
Incision type Phanansteil Low-midline Full-midline	6/10/2	7/11/0
Duration of surgery (min)	127 (29)	102 (35)
Blood loss (ml)	626 (760)	508 (302)
PEFR		
Postoperative day 1	37 (13)	41 (11)
Postoperative day 2	28 (15)	32 (17)

Results

Of the 40 patients enrolled, four (two in each group) required conversion to alternate analgesia to provide satisfactory pain relief and were excluded from analysis. Both groups were comparable with respect to age, height, weight, duration of surgery and blood loss (Table 2). The HVLC group had a slightly greater proportion of ASA III patients, and two patients in this group had full midline incisions as opposed to none in the LVHC group.

Both the HVLC and LVHC groups had low median VAS scores during both passive pain (resting) and active pain, with no difference between the groups (Fig. 1). Pain scores were generally higher with PEFR measurement compared to Oxford power assessment, but the difference did not reach significance except at a single time point (20:00 h postoperative day 1, $P=0.033$, CI 1–30).

Each study duration varied depending on the time of discharge of the patient from recovery (mean HVLC 53.75 h, LVHC 54.32 h) and ranged from a minimum of 48 h to a maximum of 58 h, data for drug consumption are therefore expressed as the mean of the individual mg h^{-1} usage (mean HVLC 8.52 mg h^{-1}, LVHC 10.57 mg h^{-1}). A scatter plot of individual patient data revealed a normal distribution, and two-tailed unpaired *t*-testing showed the HVLC group ropivacaine consumption to be significantly less than the LVHC group ($P=0.03$, CI 0.22–3.88).

The scores for nausea/vomiting, sedation, pruritus and modified Oxford on each day were averaged, and daily averaged data compared between groups (Fig. 2). Both nausea/vomiting and sedation scores were high on the day of surgery for both groups (2 and 1.9 for the HVLC group and 1.75 and 2 for the LVHC group, respectively) and progressively declined over the next 2 days. Pruritus scores were low throughout the study period. There were no differences between the groups for any of the assessed effects.

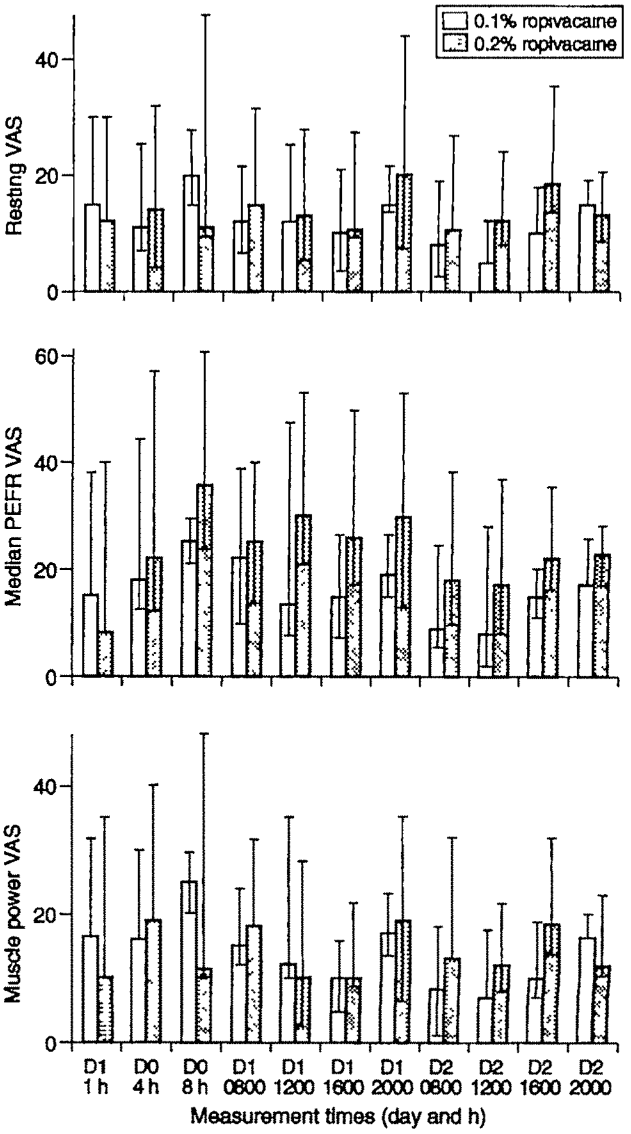

Fig 1 Visual analogue score (VAS) profiles for the 0.1% and 0 2% ropivacaine groups while at rest, during peak expiratory flow rate (PEFR) measurement and during assessment of muscle power. There were no significant differences between the groups at any of the measurement times (D0 = day of operation, D1 = first postoperative day, D2 = second postoperative day) Data are median (histogram), first and third interquartiles (error bars).

Both groups showed ~40% decrease in PEFR from the baseline on the first postoperative day, which improved to a 30% decrease by postoperative day 2 (Table 2). There were no differences between groups and inter-patient variability was marked. Modified Oxford scores demonstrated full return of quadriceps strength by the first postoperative day with minimal weakness on the day of surgery, and no difference between the groups.

There was no significant difference between the groups in sensory block assessment at any stage. Median block spread decreased with time (Table 3). However, sensory block varied markedly between patients and in the individual patient over time. Two patients in each group had no demonstrable block or pain on postoperative day 2.

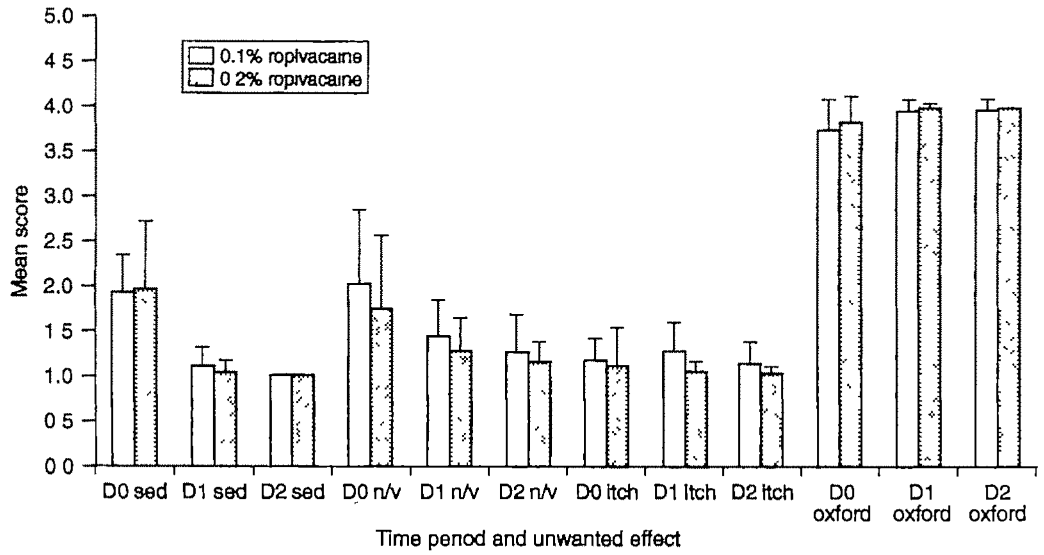

Fig 2 Unwanted effect score (sed = sedation, n/v = nausea and vomiting, itch = pruritus, oxford = muscle power) for the 0.1% and 0.2% ropivacaine groups at the measurement times (D0 = day of operation, D1 = first postoperative day, D2 = second postoperative day) There were no significant differences between the groups at any of the measurement times. Data are mean (histogram) and SD (error bars).

Table 3 Median upper and lower dermatomes achieving sensory block to pin prick at each assessed time point for both HVLC and LVHC groups. D0 = day of operation; D1 = first postoperative day, D2 = second postoperative day

	HVLC upper	LVHC upper	HVLC lower	LVHC lower
D0 1 h	T6	T5	L3	L4
D0 4 h	T7	T7	L3	L3
D0 8 h	T8	T8	L2	L2
D1 08:00 h	T9	T8	L2	L2
D1 12:00 h	T8	T8	L2	L2
D1 16.00 h	T9	T9	L2	L2
D1 20:00 h	T9	T8	L2	L2
D2 08:00 h	T9	T9	L1	L1
D2 12 00 h	T9	T10	L1	L1
D2 16:00 h	T10	T10	L1	L1
D2 20:00 h	T10	T10	L2	L1

Discussion

Treating postoperative pain following gynaecological oncology surgery with patient-controlled epidural analgesia using low-concentration ropivacaine (0.1%) with low-dose fentanyl (1 μg ml^{-1}) appears satisfactory. This study showed a significant reduction in the dose of the drug used to provide equal analgesia when the solution was high volume, low concentration compared with low volume, high concentration, thereby potentially increasing the margin between therapeutic and toxic drug levels. These findings are in accord with other workers.[8 9] In this study, active pain scores showed a good level of analgesia with the lower concentration of ropivacaine. This is contrary to the findings of several workers, but their data were collected without the addition of epidural opioid.[4 5 10] It is hypothesized that more painful stimuli penetrate an anaesthetic sleeve at lower local anaesthetic concentrations, thereby failing to provide adequate pain relief on movement and coughing.[11 12]

The incidence and severity of nausea/vomiting and sedation was high on the day of surgery. This is expected with gynaecological oncology surgery,[13] it was resolved rapidly on the first postoperative day and was virtually non-existent on postoperative day 2. As PCEA usage varied little during the study period within individual patients, it seems likely that the ropivacaine–fentanyl epidural solution did not contribute to these unwanted effects. Although the HVLC group used less drug than the LVHC group, there was no difference between groups in the incidence of side effects. Avoidance of systemic opioid may have contributed to the rapid improvement in nausea/vomiting and sedation scores. However, there was no systemic opioid group for comparison. Pruritus scores were consistently low. This may be a reflection of the small amount of fentanyl utilized by either group. Lower limb motor block was minimal and was only apparent on the day of surgery. All patients were able to stand unassisted on the first postoperative day and none of the patients who demonstrated more extensive sensory block on postoperative days 1 and 2 showed any demonstrable leg weakness, lending support to the proposition that ropivacaine produces a differential nerve block at low concentrations.[4] The reductions in PEFR in this study are comparable with others using a combined epidural–general anaesthetic technique for abdominal surgery.[14] There was no difference in PEFR reduction or the maximum upper sensory level of the epidural block achieved between the groups, supporting the view that epidural block spread is dose, rather than volume dependent.[4 10]

Epidural analgesia had to be aborted in 10% of patients during the study, which is comparable to the efficacy failure rate of epidural infusions of bupivacaine with fentanyl.[1] Two patients developed a unilateral block and two patients bilateral block failure. Complete block failure was evident on the first postoperative day despite there being adequate analgesia and sensory block on the day of surgery.

Tachyphylaxis is considered a possible cause, there being no obvious reason found at the time.

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References

1 Scott DA, Beilby DSN, McClymont C. Postoperative analgesia using epidural infusions of fentanyl with bupivacaine. *Anesthesiology* 1995; **83**: 727–37

2 Markham A, Faulds D. Ropivacaine. A review of its pharmacology and therapeutic use in regional anaesthesia. *Drugs* 1996; **52**: 429–49

3 Scott DB, Lee A, Fagan D, Bowler GMR, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth Analg* 1989; **69**: 563–9

4 Zaric D, Nydahl P-A, Philipson L, Samuelsson L, Heierson A, Axelsson K. The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2% and 0.3%) and 0.25% bupivacaine on sensory and motor block in volunteers. *Reg Anesth* 1996; **21**: 14–25

5 Scott DA, Chamley DM, Mooney PH, Deam RK, Mark AH, Hagglof B. Epidural ropivacaine infusion for postoperative analgesia after major lower abdominal surgery – a dose finding study. *Anesth Analg* 1995; **81**: 982–86

6 Slade JM. Epidural bupivacaine for aortic surgery The effect of dilution on the quality of analgesia. *Anaesthesia* 1994; **49**: 21–4

7 Etches RC, Gammer TL, Cornish R. Patient-controlled epidural analgesia after thoracotomy: a comparison of meperidine with and without bupivacaine. *Anesth Analg* 1996; **83**: 81–6

8 Kenepp NB, Cheek TG, Gutsche BB. Bupivacaine: continuous infusion epidural analgesia for labour. *Anesthesiology* 1983; **59**: A407

9 Ewen A, McLeod DD, MacLeod DM, Campbell A, Tunstall ME. Continuous infusion epidural analgesia in obstetrics. A comparison of 0.08% and 0.25% bupivacaine. *Anaesthesia* 1986; **41**: 143–7

10 Schug SA, Scott DA, Payne J, Mooney PH, Hägglöf B. Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery. *Br J Anaesth* 1996; **76**: 487–91

11 Tunstall ME, Ramamoorthy C. Continuous epidural infusion with 0.08% bupivacaine. *Anaesthesia* 1984; **39**: 939–40

12 Crawford JS. The epidural sieve and MBC (minimal blocking concentration): an hypothesis. *Anaesthesia* 1976; **31**: 1277–80

13 Chen PP, Chiu PT, Gin T. Comparison of ondansetron and metoclopramide for prevention of post-operative nausea and vomiting after major gynaecological surgery. *Eur J Anaesthiol* 1996; **13**: 485–91

14 Scott NB, James K, Murphy M, Kehlet H. Continuous thoracic epidural analgesia versus combined spinal/thoracic epidural analgesia on pain, pulmonary function and the metabolic response following colonic resection. *Acta Anaesthesiol Scand* 1996; **40**: 691–6

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Caesarean section for placenta praevia: a retrospective study of anaesthetic management

N. Parekh[1], S. W. U. Husaini[2] and I. F. Russell[3]*

[1]*Department of Anaesthesia, St James' University Hospital, Beckett Street, Leeds LS9 7TF, UK.* [2]*Department of Anaesthesia, Bradford Royal Infirmary, Bradford BD9 6RJ, UK.* [3]*Department of Anaesthesia, Hull Royal Infirmary, Kingston upon Hull HU3 2JZ, UK*

**Corresponding author*

A retrospective survey of anaesthesia for Caesarean section (CS) for placenta praevia was performed, covering the period between January 1, 1984 and December 31, 1998. Three hundred and fifty consecutive cases of placenta praevia were identified. Overall a regional technique was used 60% of the time. Five women had a placenta accreta which required Caesarean hysterectomy: one had general anaesthesia (GA) throughout and four initially received a single-shot spinal injection. Of these latter four cases, two were converted to GA during the hysterectomy and two continued with spinal anaesthesia throughout. Two other women (both GA), suffered postoperative thrombotic episodes (one pulmonary embolus and one cerebral thrombosis) but made full recoveries. Control of blood pressure when using regional anaesthesia (RA), even in the presence of considerable haemorrhage, was not a problem. Statistical regression models indicated that RA was associated with a significantly reduced estimated blood loss and reduced need for blood transfusion. This retrospective survey finds no data to support the much quoted aphorism that RA is contraindicated for CS in the presence of placenta praevia.

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Placenta praevia occurs when part of the placenta implants within the lower uterine segment. It complicates 4.8 per 1000 deliveries and is fatal in 0.03% of these.[1] It is one of the major causes of massive obstetric haemorrhage and can result in increased maternal, fetal and neonatal morbidity or mortality. In the three UK triennial maternal mortality reports from 1988 to 1996, a total of 12 maternal deaths were direct results of haemorrhage from placenta praevia.[2–4]

Anaesthesia for Caesarean section (CS) for placenta praevia is controversial. While many anaesthetists believe that general anaesthesia (GA) is mandatory for CS for placenta praevia, there is recent evidence that views may be changing.[5–8] Surveys[6–8] demonstrate a wide variation in practice among obstetric anaesthetists, with the majority (>80%) now willing to consider using regional anaesthesia (RA) for placenta praevia depending on the position of the placenta, the urgency of the situation and the extent of any continuing antenatal blood loss.[6–8] However, many respondents expressed a desire for advice on the anaesthetic management of placenta praevia.[6] Apart from anecdotal opinion,[5–10] there is little evidence on which to base such advice. Arcario and colleagues,[11] in a retrospective review of 180 patients, confirmed that RA was not necessarily contraindicated in this patient population and felt that RA techniques may decrease the estimated blood loss. In a study of maternal and perinatal morbidity resulting from 147 cases of placenta praevia, RA was used in 25% of cases with no maternal morbidity attributable to the anaesthetic techniques used.[12]

Before the widespread introduction of muscle relaxants into anaesthetic practice, placenta praevia was not viewed as a contraindication to RA. Indeed, spinal anaesthesia was viewed by some as the ideal anaesthetic. Compared with the then available GA techniques, spinal anaesthesia allowed easier intra-pelvic manipulations and uterine atony was unusual. In consequence of this latter fact, there was significantly less haemorrhage from the placental site and obstetric shock was rare with spinal anaesthesia.[13–15] However, in the 1940s the safety of spinal anaesthesia was called into question because of fears of neurological dam-

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age[16,17] and its practice in Britain virtually stopped. Around this same time muscle relaxants were introduced into anaesthetic practice. Obstetric anaesthesia based on muscle relaxants and light GA avoided most of the disadvantages of the previous spontaneously breathing inhalational GA techniques and became widely used. Subsequently, British obstetric anaesthetists had little training in, or expertise, with RA for many years, and GA became the norm for most CSs.

In recent years there has, once again, been a swing to RA for CS, with 78% of all sections now being performed under RA and, in some units, well over 90%.[18] With the paucity of published evidence available on which to base any objective recommendation, the authors' two maternity hospitals have had no firm policy on anaesthesia for placenta praevia, the technique being left to the discretion of individual anaesthetists. When this survey was initiated, about half the cases were conducted under RA. With such an even split it was felt that a retrospective analysis of our cases may provide useful information on which to base future recommendations.

Methods

In the absence of a hospital computerized obstetric database, both the hand-written labour ward register and the obstetric operating theatre register were examined and all cases where either placenta praevia or antepartum haemorrhage (APH) was recorded as a reason for CS were identified. The obstetric notes were obtained for all these patients and the cases of placenta praevia identified. The period covered by the survey was from January 1, 1984 to December 31, 1998. For each patient, the following information was recorded: gestation, parity, number of previous CSs, grade of placenta praevia, position of placenta (from ultrasound scan reports or description at surgery), the nature of the surgery (emergency or elective, as defined by the obstetrician), the anaesthetic technique used, the grade of the most senior anaesthetist present, estimated blood loss during surgery, preoperative haemoglobin (Hb) (within 24 h if there was a history of persistent vaginal bleeding), postoperative Hb (second or third postoperative day), and problems or comments noted by the anaesthetist. To compensate for blood transfused before the second venous Hb sample was obtained, the reported postoperative Hb concentrations were reduced by 1 g dl^{-1} for every unit of blood transfused.

These data were entered into a spreadsheet (Microsoft Excel v.4 for Windows NT 4.0) and analysed using SPSS (7.5.1) for Windows NT (4.0) and Genstat (v.5, release 4.1), the latter run on a mainframe computer under Unix. Depending on the data, parametric and nonparametric tests were used. The difference between preoperative and postoperative Hb was analysed using multiple regression with backward elimination of factors to select the final model (Genstat). Because of the known inaccuracies of estimating blood loss, the estimated volumes were grouped into the following categories: ≤500, 501–1000, 1001–1500, 1501–2000 and ≥2000 ml. There were only seven patients in the ≥2000 ml group, too few for statistics to be meaningful, these seven patients were amalgamated with the 1501–2000 ml group and the data were analysed using proportional-odds ordinal regression, again with backward elimination to select the final model (Genstat). Transfusion requirements were analysed using a Poisson regression model with backward elimination of factors to select the final model (Genstat). $P<0.05$ was taken as indicating statistical significance.

Table 1 The grade of placenta praevia, the nature of surgery and the anaesthetic technique used. El=elective Caesarean section. Em=emergency Caesarean section, GA=general anaesthesia; RA=regional anaesthesia; RA%=regional anaesthesia as a percentage of the total number of anaesthetics *Includes one case where spinal anaesthesia was performed but failed to spread adequately, so GA was given **Includes one case of spinal anaesthesia for Caesarean section, GA for hysterectomy ***Includes one case of spinal anaesthesia for Caesarean section and hysterectomy

	Grade 1		Grade 2		Grade 3		Grade 4		Total
	El	Em	El	Em	El	Em	El	Em	
GA	6	14	7	29*	13	43*	6	22	140
RA	20***	19	48**	20	44***	26	21**	12	210
RA%	77	58	87	41	77	38	78	35	60

Results

Three hundred and fifty consecutive cases of placenta praevia progressing to CS were identified from January 1, 1984 to December 31, 1998 inclusive. Table 1 shows the type of surgery and the grade of placenta praevia. Overall 210 CSs (60%) were performed with a RA technique. Table 2 shows the grade of the most senior anaesthetist present, the type of anaesthetic, conversions of one anaesthetic technique to another and the nature of the CS.

There were 140 women with an anterior placenta praevia; 31 of these had experienced a previous CS. Only two of the latter proceeded to hysterectomy (Table 3). In total, there were seven cases of placenta accreta of which five progressed to hysterectomy (Table 3). Two of these women had a spinal anaesthesia for their CS and GA for their hysterectomy because the spinal anaesthesia wore off as a result of delay in performing the hysterectomy. In the two remaining spinal anaesthesia cases there was no delay in proceeding to hysterectomy; in both cases the spinal anaesthesia provided anaesthesia sufficient for the total duration of the surgery.

As regards anaesthetic problems, in addition to the information in Table 2, there were four cases where it took 'multiple attempts' to place spinal anaesthesia successfully; one potentially difficult intubation was avoided by the use of an epidural; two women known to have had previous problems with suxamethonium (scoline apnoea; cardiac arrest following extreme bradycardia unresponsive to

Table 2 The grade of the most senior anaesthetist present and type of anaesthesia used for emergency or elective Caesarean section for placental praevia. GA=general anaesthesia †Includes one failed spinal anaesthesia converted to GA before delivery. ‡Includes two spinal anaesthesias for Caesarean section with GA for hysterectomy, one failed epidural converted to spinal anaesthesia preoperatively and two spinal anaesthesias for Caesarean section and subsequent hysterectomy. ‡‡Includes one Caesarean section proceeding to hysterectomy ††Includes one combined spinal–epidural anaesthetic **Includes one combined spinal–epidural anaesthetic where the spinal component failed to spread and the epidural was topped up preoperatively

	Emergency Caesarean section			**Elective Caesarean section**			**Total**
	GA	**Spinal**	**Epidural**	**GA**	**Spinal**	**Epidural**	
Consultant	12	20	6	13‡‡	53‡	13**	117
Associate specialist	4†	2	0	2	10		18
Senior registrar	4	1		2	7		14
Staff anaesthetist	3	5	1	0	2	0	11
Registrar	55	19††	5	10	20	9	118
SHO/clinical assistant	35†	11††	2**	5	11	8	72
Total	113	58	14	32	103	30	350

Table 3 The seven cases of placenta accreta with their management. CS=Caesarean section, El=elective Caesarean section, Em=emergency Caesarean section; GA=general anaesthesia throughout; Sp=spinal anaesthesia throughout, Sp/GA=spinal for Caesarean section with GA for hysterectomy

Position of placenta	**Previous CS**	**El/Em**	**Anaesthetic**	**Most senior anaesthetist present**	**Hysterectomy**	**Total units of blood transfused**
Anterior	no	El	Sp	consultant	yes	4
Anterior	no	El	GA	consultant	no	4
Anterior	yes	El	Sp/GA	consultant	yes	28
Anterior	yes	El	GA	consultant	yes	5
Posterior	yes	El	Sp/GA	consultant	yes	3
Posterior	yes	El	Sp	consultant	yes	2
Anterior	no	Em	GA	staff doctor	no	2

atropine 1.2 mg) received spinal anaesthesia; one difficult intubation was encountered during induction of GA in an emergency case; there were two cases of oxygen desaturation during GA (one of these was eventually diagnosed as being caused by endobronchial intubation, while the other remained cyanosed throughout surgery despite various attempted remedies); one patient with known malignant hyperpyrexia received total intravenous anaesthesia. Two other GA cases had thrombotic episodes postoperatively. The first of these patients had GA for her CS where placenta accreta was encountered. Surgery proceeded directly to subtotal hysterectomy after delivery of the infant. Over a 24 h period, this patient received 6500 ml crystalloid, 2000 ml colloid and 5 units of blood. Her subsequent recovery was complicated by intermittent pyrexia, abdominal pain, chest tightness, dizziness and the development of a broad ligament haematoma. She was eventually discharged on day 14 but then on day 18 she was admitted as an emergency to the chest unit following a pulmonary embolus for which she was given anticoagulant. The second patient, with a grade IV placenta praevia, had an uneventful CS under GA and an uncomplicated postoperative period while in hospital. Then, on day 13, she awoke at home with a severe headache and a left hemiparesis. An MRI scan revealed an infarct caused by arterial thrombosis deep within the right hemisphere. Both women made full recoveries.

Hypotension was a specific problem recorded in 13 women undergoing RA: eight procedures were elective (five spinal anaesthetics, one combined spinal epidural (CSE), two epidurals) and five were emergency (three spinal anaesthetics, two CSE). In none of these cases was the hypotension related to blood loss. In 11 cases, hypotension occurred during the initial induction of the block. In the two remaining cases, hypotension occurred shortly after delivery and was associated with uterine manipulation. In neither case did it cause any concern. The average estimated blood loss during surgery in these 13 women was 600 ml (range 200–1500 ml). Only one of these women received a blood transfusion. Hypotension was a specific problem in seven GA patients (five emergency, two elective) and was always associated with intra-operative bleeding. The average estimated blood loss in this subgroup of seven women was 1600 ml (range 500–3500 ml). All but one of these women received a blood transfusion.

One hundred and eighty five cases (53%) were classified as either emergency or urgent and in the majority of these (69%) anaesthesia was performed by a registrar or SHO grade anaesthetist. There was a highly significant difference between the anaesthetic techniques used by consultants and trainees in emergency cases: trainees used GA 71% of the time, compared with 40% for consultants (chi-squared $P=0.0005$). With regard to the elective cases, although there was a similar trend with GA being used for 17 and 24% of cases by consultants and trainees, respectively, the difference was not statistically significant (chi-squared $P=0.25$).

Analysis of the haematological information was complicated by the fact that women received blood transfusions at various times, before during or after the operation. For 11 women who had received 5–28 units of blood it

Table 4 The estimates (i e. beta values), with their standard errors, for the variables which were found to be statistically ($P<0\ 05$) associated with estimated blood loss (proportional odds ordinal regression modeling) Cut point 0/1, ≤500 ml; cut point 1/2, ≤1000 ml; cut point 2/3, ≤1500 ml

	Estimate (SE)
Cut point	
0/1	8 31 (2 65)
1/2	10 29 (2.67)
2/3	11.26 (2.68)
Year	0.0936 (0 0293)
Regional anaesthesia	–0.082 (0 242)
Position of placenta	
Posterior	–0.570 (0.235)
Central	–0 259 (0 661)
Lateral	–0 212 (0 598)
Grade of placenta praevia	
II	0 09 (0.346)
III	0 312 (0.331)
IV	0.824 (0 401)

Table 5 The estimates (i.e. beta values), with their standard errors, for the variables which were found to be statistically ($P<0.05$) associated with blood transfusion requirements (Poisson regression modelling)

	Estimate (SE)
Constant	3 106 (0.729)
Gestation	–0 0826 (0.0208)
Regional anaesthesia	–1.074 (0 173)
Position of placenta	
Posterior	–0.446 (0.155)
Central	–0 706 (0.407)
Lateral	–1 129 (0 707)
Grade of placenta praevia	
II	–0 311 (0 231)
III	–0.340 (0.22)
IV	0.469 (0 219)

was not possible to ascertain when the preoperative and postoperative blood samples were obtained in relation to the blood transfusions they received. The data for these 11 women (7 emergency, 4 elective) were excluded in the analysis of differences between preoperative and postoperative Hb concentrations but included in all other analysis.

After all the data had been entered into the relevant stepwise regression procedures, the only variables that showed a statistically significant predictive relationship with estimated blood loss were the anaesthetic (GA or RA), the position of the placenta, the grade of the praevia and the year of surgery. For blood transfusion requirements, the significant variables were the anaesthetic (GA or RA), the position of the placenta, the grade of praevia and the gestation. These variables and the equations created by the regression statistics are shown in Tables 4 and 5. No statistically significant variables were associated with the difference between preoperative and postoperative Hb concentration.

Mean estimated blood loss (SD) for all patients in the study was 672 (441) ml; for RA patients only it was 613 (367) ml and for GA patients only it was 756 (518) ml (95% confidence interval for the difference between the means was 41–244 ml; $P=0.006$).

Discussion

Recent surveys have indicated, that while many anaesthetists are willing to use RA for CS for placenta praevia, others would not do so under any circumstances.[6–8] A desire has been expressed for advice on the anaesthetic management of placenta praevia[6] but there is a lack of published evidence on which to base any objective advice. Arcario and colleagues,[11] in a retrospective review of 180 patients, felt that RA was not necessarily contra-indicated in this patient population and that RA techniques may, in fact, decrease the estimated blood loss at surgery for simple placenta accreta. However, their study, which was presented in abstract only, provided few other details. McShane, Heyl and Epstein,[12] in a retrospective study of 147 cases of placenta praevia, reported briefly that RA had been used in 25% of cases and that there was no maternal morbidity attributable to the anaesthetic techniques used. Our current, more detailed, retrospective study of anaesthesia for 350 cases of placenta praevia provides further evidence to complement these two studies. We found no significant permanent morbidity associated with any of the anaesthetic techniques and, like Arcario and colleagues,[11] we noted a significantly lower estimated blood loss in the RA group. Unlike the two previous studies,[11 12] our data allowed us to apply regression statistics to control for the many interacting factors affecting blood loss. This process clearly indicated that, compared with GA, RA was associated with a significantly lower estimated blood loss and lower transfusion requirements, whatever the classification of the CS or the grade of placenta praevia.

It is accepted that estimating blood loss during CS is notoriously inaccurate and this was the reason for the broad groupings of estimated blood loss. Despite the inaccuracies, the estimates are probably a useful indicator of how concerned the anaesthetist or surgeon was during the procedure. At the same time it must be recognized that estimated blood loss and, hence, the need for blood transfusion may be biased by the beliefs of the anaesthetist or obstetrician. Those with confidence in RA may make lower estimates of blood loss which, in turn, may influence the blood transfusion rate. However, if patients were being systematically undertransfused in the RA group, this would be revealed in the postoperative Hb concentrations. There is no evidence from the data that the RA group were undertransfused since, compared with the GA group, the RA group had a similar mean preoperative Hb concentration, a lower rate of blood transfusion, a similar mean postoperative Hb concentration, and a similar preoperative–postoperative Hb difference.

While massive haemorrhage is a recognized complication of placenta praevia, there was no evidence from this survey to indicate that the management of such haemorrhage was a problem under RA. Those who advocate GA for placenta praevia fear that the sympathetic blockade induced by RA will make it difficult or impossible to control arterial pressure should severe haemorrhage occur. In our survey, ephedrine was the only sympathomimetic drug required, except in one patient. While it is accepted that inducing RA in the presence of uncorrected hypovolaemia may be fraught with problems, the physiological responses to haemorrhage when haemorrhage first occurs after RA has been safely established is a very different scenario. In this latter situation, in contrast to GA, RA may provide a protective effect.[19 20] The normal intense vasoconstriction associated with significant blood loss is not possible with RA and the arterial pressure is much more dependent on intravascular fluid volume than during GA. During light GA, the brisk sympathetic reflexes may maintain arterial pressure in the face of significant continuing blood loss and lead the less experienced anaesthetists and surgeons to underestimate blood loss and undertransfuse until circulatory collapse suddenly occurs. The intense vasoconstriction during such light GA may also be detrimental to organ perfusion and oxygenation and may predispose the mother to major organ failure in the postoperative period. When dogs are bled after induction of high thoracic epidural anaesthesia, there is significantly better survival than if the animals are bled to a similar degree in the absence of epidural anaesthesia (9/10 compared with 2/10 survival, respectively).[19] The dogs in the thoracic epidural group had slower heart rates, greater cardiac stroke volume, higher arterial pH and bicarbonate concentration, and lower catecholamine and lactate concentrations than the GA controls.[19] Further evidence of some protection from the effects of haemorrhage by epidural anaesthesia can be found in sheep: epidural anaesthesia attenuated the increase in uterine vascular resistance associated with haemorrhage.[20]

Some may have anxieties regarding the management of heavy blood loss in conscious patients but this retrospective review did not highlight any concerns about anaesthesia. Seven women had an estimated blood loss of >35–40% of their estimated blood volume. Of these women, five had GA from the outset because of significant APH, so consciousness was not an issue; one primigravid patient with an anterior grade III placenta praevia received a spinal anaesthetic and subsequently lost an estimated 3000 ml of blood but, as this was replaced rapidly with warmed blood and other fluids, no untoward effects were observed. Only one mother had symptoms related to blood loss; this woman, with two previous CSs and a grade II anterior placenta praevia, had a spinal anaesthetic and lost an estimated 6000 ml over the 60 min duration of her CS.

Another possible area of concern in relation to RA, particularly spinal anaesthesia, is the duration of surgery. In our survey, technical problems aside, duration of an adequate block from either a spinal or epidural anaesthetic for CS for placenta praevia was not a problem.

In two prospective studies of anaesthesia for Caesarean hysterectomy, 24 of 60[21] and seven of 28[22] cases initially commenced under RA required conversion to GA. In the study by LaPlatney and O'Leary,[21] four of 18 spinal anaesthetics required 'inhalational supplementation' and two of these developed aspiration pneumonitis (from the data it is not clear if 'inhalational supplementation' is equivalent to intubation and formal GA or merely as it says, 'inhalational supplementation'). This led the authors to comment that GA should be considered preferable.[21] On the other hand Chestnut and Redick[22] felt that women should not be prohibited from choosing epidural anaesthesia for Caesarean hysterectomy and, in a prospective study of Caesarean hysterectomy, Chestnut and colleagues,[23] using RA in 13 of 45 cases, stated that they believed elective Caesarean hysterectomy was not a contraindication to epidural anaesthesia.

It is not clear why the year of surgery was positively correlated with an increased estimate of blood loss. This apparent correlation could have been caused by chance or the year may be a proxy indicator for some other factor (perhaps related to changes in medical staffing on the labour ward). Unfortunately, information on the duration of surgery and the grade of operator was not collected in our survey.

Whatever the anaesthetic technique, it is essential that plans are made to contend with sudden blood loss. If the mother is to be awake, then the possible need for rapid fluid or blood replacement should be explained preoperatively to reduce anxiety should the need for such infusions arise. In the absence of prospective randomized trials, it is difficult to find objective evidence on which to base the arguments for or against GA or RA for placenta praevia. However, this retrospective analysis of anaesthesia for placenta praevia finds no evidence to support the much quoted opinion that GA is mandatory in such cases. Indeed, to the contrary, this study adds to the growing literature[11 12 22 23] suggesting that, when RA is used, not only is there no reduction in maternal safety in relation to the management of blood loss but there may be a reduced blood loss and reduced need for postoperative blood transfusion.

References

1 Iyasu S, Saftlas AK, Rowley DL, Koonin LM, Lawson HW, Atrash HK. The epidemiology of placenta previa in the United States, 1979 through 1987. *Am J Obstet Gynecol* 1993; **168**: 1424–9

2 Department of Health, Welsh Office, Scottish Office Home and Health Department; Department of Health and Social Services, Northern Ireland. *Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1988–90.* London: HMSO, 1994

3 Department of Health, Welsh Office, Scottish Office Home and Health Department; Department of Health and Social Services, Northern Ireland. *Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1991–93.* London: HMSO, 1996

4 Department of Health, Welsh Office, Scottish Office Department of Health, Department of Health and Social Services Northern Ireland. *Why Mothers Die. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1994–96.* London: The Stationery Office, 1998

5 Tunstall ME. Section 1. Discussion. In: Reynolds F, ed. *Epidural and Spinal Blockade in Obstetrics*. London: Baillière Tindall, 1990; 35–7

6 Bonner SM, Haynes SR, Ryall D. The anaesthetic management of Caesarean section for placenta praevia: a questionnaire survey. *Anaesthesia* 1995; **50**: 992–4

7 Peel WJ. A survey of the anaesthetic management of patients presenting for Caesarean section with 'high risk' obstetric conditions. *Int J Obstet Anaesth* 1996; **5**: 219–20

8 Plumer MH, Rottman R. How anesthesiologists practice obstetric anesthesia. Responses of practicing obstetric anesthesiologists at the 1993 meeting of the Society for Obstetric Anaesthesia and Perinatology. *Reg Anesth* 1996; **21**:49–60

9 Bromage PR. *Epidural Analgesia*. Philadelphia: WB Saunders, 1978.

10 Crawford JS. *Obstetric Analgesia and Anaesthesia*. Edinburgh: Churchill Livingstone, 1984; 109–10

11 Arcario T, Greene M, Ostheimer GW, Datta S, Naulty JS. Risks of placenta praevia/accreta in patients with previous Caesarean deliveries. *Anesthesiology* 1988; **69** (Suppl 3A): A659

12 McShane PM, Heyl PS, Epstein MF. Maternal and perinatal morbidity resulting from placenta praevia. *Obstet Gynecol* 1985; **65**: 176–82

13 Thomas RC. Caesarean section under spinal analgesia. *J Obst Gynaec Brit Emp* 1942; **49**: 247–74

14 Resnick L. Heavy nupercaine spinal analgesia in operative obstetrics. *Br Med J* 1945; **24**: 722–3

15 Thomas RC. Caesarean section under spinal analgesia. *J Obst Gynaec Brit Emp* 1944; **51**: 324–9

16 Kennedy F, Effron AS, Perry G. The grave spinal cord paralyses caused by spinal anaesthesia. *Surg Gynec Obstet* 1950; **91**: 385–98

17 Cope RW. The Wooley and Roe Case. Wooley and Roe versus the Ministry of Health and others. *Anaesthesia* 1954; **9**: 249–70

18 Shibli ?, Russell ? *authors to add details*

19 Shibata K, Yamamoto Y, Murakami S. Effects of epidural anesthesia on cardiovascular responses and survival in experimental hemorrhagic shock in dogs. *Anesthesiology* 1989; **71**: 953–9

20 Vincent RD, Chestnut DH, McGrath JM, Chatterjee P, Poduska DJ, Atkins BL. The effects of epidural anesthesia on uterine vascular resistance, plasma arginine vasopressin concentration, and plasma renin activity during hemorrhage in gravid ewes. *Anesth Analg* 1994; **78**: 293–300

21 La Platney DR, O'Leary JA. Anesthetic considerations in Cesarean hysterectomy. *Anesth Analg* 1970; **49**: 328–30

22 Chestnut DH, Redick LF. Continuous epidural anesthesia for elective Cesarean hysterectomy. *South Med J* 1985; **78**: 1168–9

23 Chestnut DH, Dewan DM, Redick LF, Caton D, Spielman FJ. Anesthetic management for obstetric hysterectomy: a multi-institutional study. *Anesthesiology* 1989; **70**: 607–10

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Does wound irrigation with triamcinolone reduce pain after surgery to the lumbar spine?

L. H. Pobereskin and J. R. Sneyd[1]*

Department of Neurosurgery and [1]Department of Anaesthesia, Derriford Hospital, Plymouth PL6 8DH, UK
**Corresponding author*

This prospective, randomized study compared postoperative pain scores, morphine consumption and length of stay in 95 adults who underwent elective lumbar spine surgery via a posterior incision. Immediately prior to closure the wound was irrigated with triamcinolone 40, 20 or 0 mg. Visual analogue scale pain scores at 24 h after surgery were median 12 (interquartile range 3–24), 15 (6–34) and 33 (20–59) mm for patients receiving triamcinolone 40, 20 mg or no steroid, respectively ($P<0.0005$, Kruskal–Wallis test). Total morphine usage after 24 h was 26 (21–39), 27 (17–43) and 43 (27–73) mg for the same groups ($P<0.001$, Kruskal–Wallis test). The proportion of patients discharged from hospital on the first day after surgery was 83.9, 77.4 and 54.8% for patients receiving triamcinolone 40, 20 mg and no steroid, respectively ($P<0.028$, chi-squared test). Extra-dural triamcinolone reduces pain after lumbar spine surgery and reduces time to discharge from hospital.

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Pain after surgery is distressing for patients and may delay their mobilization. Although the use of opiate analgesia for pain relief is widespread, its uptake by patients may be limited by side effects, notably nausea, vomiting and sedation. Although wound infiltration with bupivacaine towards the end of surgical procedures on the lumbar spine is commonly undertaken, reports on its efficacy are equivocal.[1–7] We have previously reported that in a non-random subset of patients to whom extra-dural steroid was administered during wound closure, there was a significant reduction in pain after surgery.[1] However, this was an unexpected finding in a *post hoc* analysis of data from an investigation of the efficacy of para-vertebral wound infiltration with bupivacaine. The present study was designed to rigorously and prospectively investigate the efficacy of extra-dural triamcinolone as an adjuvant therapy to reduce pain after surgery to the lumbar spine.

Methods

All patients admitted to the Department of Neurosurgery at Derriford Hospital, Plymouth, UK in anticipation of surgery for benign conditions of the lumbar spine were approached to participate in this trial. Written consent was obtained. Patients who were under 18, pregnant, or in whom it was expected that the dura would be opened were excluded. Prior approval was obtained from the South and West Devon Health Authority Ethics Committee. In addition, as extra-dural administration of triamcinolone is not a licensed indication, we obtained a Clinical Trials Exemption certificate (CTX) from the Medicines Control Agency of the UK.

Patients were pre-medicated with temazepam 10–20 mg and anaesthetized with propofol and fentanyl, 2 $\mu g\ kg^{-1}$ followed by 0.5–1.5% isoflurane (end tidal concentration) and 66% N_2O in oxygen administered by mechanical ventilation. Additional fentanyl was given as clinically indicated. Paralysis was achieved with vecuronium or atracurium, and reversed at the end of surgery using glycopyrronium and neostigmine. Droperidol 0.5 mg was given as a prophylactic anti-emetic.

Treatment allocation (40, 20 or 0 mg triamcinolone) was determined by a computer-generated randomization scheme. Study allocation was held in individually numbered sealed opaque envelopes which were not opened until after the surgical procedure had been completed and wound closure was about to commence. If the dura was inadvertently opened before the end of the surgical procedure, the patient was not randomized.

Triamcinolone injection is an opaque white suspension, and after discussion with the pharmacy we could not identify a suitable inert substance with a similar appearance which

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could be safely administered as a placebo. It was therefore not possible to blind the operating surgeon or the operating room staff. However, implementation of the standardized prescriptions for postoperative analgesia and collection of outcome data were the responsibility of nursing staff who were blind to the treatment allocation.

The study protocol dictated randomization only immediately prior to wound closure. This allowed the exclusion of patients in whom the dura was inadvertently opened and also ensured that the administration of the standardized anaesthetic was not biased by prior knowledge of the patient's treatment allocation. Anaesthetic interventions after administration of study drug were limited to reversal of neuromuscular block and extubation. No additional fentanyl was administered after wound closure had commenced.

All patients were operated on in the prone position on an extension frame. Before surgical incision, the skin and subcutaneous tissues were infiltrated with 20 ml 1% lidocaine with epinephrine 1/200 000. Immediately prior to wound closure, the randomization envelope was opened, and according to the instructions inside, triamcinolone 40, 20 mg or no steroid was placed in the wound under direct vision. The triamcinolone (40 mg ml^{-1}) was drawn up in a sterile 1-ml syringe and infused in such a way as to coat the paraspinal muscles and drain down into the extradural space.

In the postoperative recovery area, patients received i.v. morphine 2 mg at 5-min intervals until comfortable, and subsequently used a patient control analgesia (PCA) system with morphine 50 mg and droperidol 2.5 mg diluted to 50 ml with 0.9% saline. The system was set to give a bolus injection of 1 ml (containing morphine 1 mg and droperidol 50 μg) with a lockout period of 5 min and no background infusion.

After giving written informed consent, preoperative variables including age, gender, weight, duration of symptoms, operative indication and preoperative pain scores (VAS) were recorded. A baseline pain score was obtained from the patient using a 100-mm visual analogue scale (VAS) ranging from 'no pain' to 'the worst pain I can imagine'. It was emphasized that we were collecting data on spinal pain only, not radicular symptoms.

Operative variables recorded included the number of levels operated upon, the length of the incision, the duration of the operation, the grade of operating surgeon, whether the operation was unilateral or bilateral, and the dose of fentanyl.

Outcome measures collected were pain scores (VAS), 24 h morphine usage and length of stay. VAS pain scores were recorded at 3, 12 and 24 h by nurses blinded to the study drug. Again it was emphasized that we were scoring spinal pain not radicular symptoms. At 24 h, total morphine consumed during the postoperative period was read from the PCA machines and this was added to the morphine given in the recovery room to obtain 24 h morphine usage. Decisions on discharge were made according to strict criteria by doctors, physiotherapists and nurses blinded to study allocation. Patients were discharged when they were independent for self-care, fully mobile including the stairs, comfortable on oral non-opioid analgesics, and able to pass urine unaided. Decisions about patient discharges were made during a ward round on the morning immediately after surgery.

Statistical analysis was undertaken with SPSS for Windows Version 8.0 on a personal computer. The three groups were compared with a one-way ANOVA or Kruskal–Wallis test for continuous variables as appropriate. The Bonferroni method was used to correct for multiple comparisons. Categorical variables were compared with the chi-squared test. To evaluate any dose–response relationship between study group and outcome, the chi-squared test for trend and polynomial linear contrasts (ANOVA) were used. Factorial analysis of variance was used to test the influence of certain preoperative factors on outcome. Pain scores at 24 h and total morphine consumption end-points were not normally distributed, so these variables were square root transformed prior to factorial analysis of variance and polynomial linear contrasts. The null hypothesis was rejected when $P<0.05$.

Sample size was determined by an *a priori* power calculation based on our earlier study of patients undergoing lumbar spine surgery.[1] We felt the smallest clinically significant difference in VAS scores and morphine usage over 24 h would be 15 mm and 15 mg, respectively. Three groups of 31 patients were sufficient to detect both these differences with an alpha error of 0.05 and a power of 80%.

Results

One hundred and two consecutive patients were approached to participate in the trial and all gave consent. Two patients suffered a CSF leak during the procedure and there was no PCA apparatus available for another three. On two occasions the protocol was violated when an analgesic (diclofenac) was prescribed as a part of premedication. None of these seven patients was randomized. Two patients were randomized to triamcinolone 20 mg but did not complete the protocol. One became hypotensive and the morphine PCA was discontinued, and one was given diclofenac (an accidental protocol violation) during the first 24 h. These two patients were excluded from subsequent analysis. Ninety-three patients completed the trial and full data sets were available for all of them.

Patient characteristics and preoperative pain scores for the 93 evaluable patients are shown in Table 1. The patients who received triamcinolone had a shorter duration of symptoms and lower preoperative pain scores than those who did not receive steroid. However, these differences were not statistically significant.

Operative variables are summarized in Table 2. The incision length was slightly longer in the group that did not receive steroid but this was not statistically significant. All

Table 1 Patient characteristics, duration of symptoms and preoperative pain scores. Data are mean (SD or range) or number *One-way ANOVA. **Chi-squared

	No steroid ($n=31$)	Triamcinolone 20 mg ($n=31$)	Triamcinolone 40 mg ($n=31$)	P-values
Age (yr)	44.5 (23.3–78.5)	44.8 (22.7–69.7)	46.3 (24.0–76.6)	0.904*
Sex (M/F)	18/13	17/14	12/19	0.264**
Weight (kg)	74.1 (15)	74.6 (15.7)	78.3 (13.4)	0.484*
Duration of symptoms (months)	16.8 (14.4)	13.8 (13)	11 (9.6)	0.206*
Preoperative pain score (mm)	52.9 (23.6)	44.3 (28.8)	38.2 (30.2)	0.117*

Table 2 Duration of surgery and details of surgical procedure. Data are mean (SD) or number *One-way ANOVA. **Chi-squared. ***Kruskal–Wallis test

	No steroid ($n=31$)	Triamcinolone 20 mg ($n=31$)	Triamcinolone 40 mg ($n=31$)	P-values
Incision length (cm)	6.3 (2.6)	4.8 (1.1)	5.1 (2)	0.07***
Duration of surgery (min)	68.1 (28.8)	62.4 (26.7)	62.4 (24.6)	0.656*
Levels operated upon	1.2 (0.51)	1.1 (0.37)	1.1 (0.45)	0.623*
Bilateral/unilateral	6/25	3/28	5/26	0.555**

Table 3 Visual analogue pain scores (VAS), morphine usage and duration of hospital stay after lumbar spine surgery. Data are percentage, mean (SD) or median (interquartile range). *One-way ANOVA. **Chi-squared ***Kruskal–Wallis test. †ANOVA polynomial linear contrasts (square root transformation for 24 h pain scores and total morphine usage). ‡Chi-squared for trend

	No steroid ($n=31$)	Triamcinolone 20 mg ($n=31$)	Triamcinolone 40 mg ($n=31$)	Between group differences (P-values)	Dose–response relationship (P-values)
VAS (3 h)	41.1 (26.2)	38.1 (25.6)	29.3 (19.4)	0.126*	0.056†
VAS (12 h)	32.9 (18.7)	28 (20.8)	23.6 (18.4)	0.174*	0.062†
VAS (24 h)	33 (20–59)	15 (6–34)	12 (3–24)	0.0005***	0.001†
24 h morphine usage (mg)	43 (27–73)	27 (17–43)	26 (21–39)	0.001***	0.007†
Length of stay (days)	1.48 (0.57)	1.22 (0.42)	1.16 (0.37)	0.025***	0.007†
Discharged on first day after surgery (%)	54.8	77.4	83.9	0.028**	0.011‡

other measures of operative complexity of the three groups were comparable.

Table 3 shows the outcome variables. There was no significant difference in pain scores at 3 or 12 h after surgery. Twenty-four hour pain score, 24 h morphine usage, length of stay and the probability of being discharged from hospital more than 24 h after surgery were all significantly lower in patients who had received triamcinolone than in those who had not (ANOVA). *Post hoc* analysis showed that both the groups which received 20 or 40 mg of triamcinolone were significantly different from the group that received no steroid ($P<0.05$), but they were not different from each other. Tests for trend show a significant linear dose–response relationship for all outcome variables except VAS at 3 and 12 h. The results for these two variables are only just outside statistical significance.

Despite rigorous randomization, there were some interesting, albeit, non-significant differences between groups in terms of preoperative factors. In view of the lower preoperative pain scores and shorter histories in those patients who received steroids (Table 1), additional statistical analysis was carried out to explore the possibility that preoperative differences in the study groups may have contributed to our findings. In a factorial analysis of variance with 24 h morphine consumption as the dependent variable, steroid group as a co-factor and both preoperative VAS score and length of history as co-variants, only the steroid group significantly predicted outcome. The same result was obtained when 24 h VAS was used as the dependent variable.

Discussion

The efficacy of epidural injection of steroids for selected patients with sciatica is well established.[8] However, their use is not without risk and reported complications include infection[9] and paralysis.[10] Extra-dural administration of triamcinolone with lidocaine in a cat model did not cause significant damage to neural tissues.[11] Extra-dural administration of steroids after surgery to the lumbar spine reduces postoperative fibrosis in an animal model,[12] and individual neurosurgeons have used steroids in this way for some years although the practice is not universal.

Few studies have investigated whether triamcinolone can modify acute pain outwith the spine. Local injection of steroid into the pillar of the fauces and the tonsil bed reduces pain after tonsillectomy.[13] However, adding triamcinolone to bupivacaine did not reduce postoperative morphine consumption in men undergoing elective inguinal hernia repair under general anaesthesia.[14] Some small studies have evaluated the use of extra-dural steroids to relieve pain after spinal surgery. In a non-randomized study, Foulkes and Robinson reported that 22 patients who received wound irrigation with dexamethasone acetate suspension 16 mg after lumbar hemi-laminectomy or micro-discectomy used less narcotics than historic controls.[15] Ang and colleagues[16] randomized patients to receive extra-dural dexamethasone 4 mg or no steroid after 'lumbar lamino-arthrectomy' and reported that the steroid group experienced less pain and requested less pentazocine than the controls. Our study confirms these findings and extends them to suggest a dose–response relationship with the higher 40 mg dose of triamcinolone giving the greatest reduction in pain scores and morphine usage. We found no statistically significant effect of triamcinolone at 3 and 12 h after surgery, although the pain scores at these times were lower amongst those patients who had received steroid. The smallest difference between groups was 9 mm at 12 h. If this was to be considered clinically significant it would have taken three groups of 85 patients to test the hypothesis that such a difference was statistically significant.

Although the use of steroid after lumbar hemi-laminectomy or micro-discectomy has previously been shown to reduce hospital stay from an average of 8.7 to 6.4 days,[15] the relevance of such findings to modern surgical practice with aggressive early discharge was unknown. We have demonstrated that triamcinolone offers a shorter stay in hospital and an increased chance of discharge on the first day after surgery when early discharge protocols are already routine.

This prospective, randomized, controlled study has rigorously tested the hypothesis that wound infiltration with triamcinolone can reduce pain after surgery to the lumbar spine, and has demonstrated an effect which is both statistically and clinically significant. In support of this finding is a dose–response relationship for all outcome variables. Additional work might usefully determine the optimum dose of triamcinolone, although this might require an unfeasibly large number of patients.

References

1 Chadduck JB, Sneyd JR, Pobereskin LH. The role of bupivacaine in early postoperative pain control after lumbar decompression. *J Neurosurg (Spine 1)* 1999; **90**: 67–72

2 Teddy PJ, Fabinyi GC, Kerr JH, *et al.* Bupivacaine infiltration after lumbar laminectomy. Local infiltration in the control of early postoperative lumbar laminectomy pain. *Anaesthesia* 1981; **36**: 380–3

3 Rechtine GR, Love LC. Postoperative laminectomy pain control using bupivacaine and epidural morphine. *Orthopedics* 1986; **9**: 1711–2

4 Mullen JB, Cook WAJ. Reduction of postoperative lumbar hemilaminectomy pain with Marcaine. Technical note. *J Neurosurg* 1979; **51**: 126–7

5 Milligan KR, Macafee AL, Fogarty DJ, *et al.* Intraoperative bupivacaine diminishes pain after lumbar discectomy. A randomised double-blind study. *J Bone Joint Surg* (*British Volume*) 1993; **75**: 769–71

6 Glasser RS, Knego RS, Delashaw JB, *et al.* The perioperative use of corticosteroids and bupivacaine in the management of lumbar disc disease. *J Neurosurg* 1993; **78**: 383–7

7 Cherian MN, Mathews MP, Chandy MJ. Local wound infiltration with bupivacaine in lumbar laminectomy. *Surgical Neurol* 1997; **47**: 120–2; discussion 122–3

8 Watts RW, Silagy CA. A meta-analysis on the efficacy of epidural corticosteroids in the treatment of sciatica. *Anaesth Intens Care* 1995; **23**: 564–9

9 Cooper AB, Sharpe MD. Bacterial meningitis and cauda equina syndrome after epidural steroid injections. *Can J Anaesth* 1996; **43**: 471–4

10 McLain RF, Fry M, Hecht ST. Transient paralysis associated with epidural steroid injection. *J Spinal Disord* 1997; **10**: 441–4

11 Delaney TJ, Rowlingson JC, Carron H, *et al.* Epidural steroid effects on nerves and meninges. *Anesth Analg* 1980; **59**: 610–4

12 Hinton JLJ, Warejcka DJ, Mei Y, *et al.* Inhibition of epidural scar formation after lumbar laminectomy in the rat. *Spine* 1995; **20**: 564–70; discussion 579–80

13 Liu CM, Su CY. Post-operative pain control with topical steroid injection after hot dissection tonsillectomy. *J Laryngol Otol* 1996; **110**: 1038–40

14 McCleane G, Mackle E, Stirling I. The addition of triamcinolone acetonide to bupivacaine has no effect on the quality of analgesia produced by ilioinguinal nerve block. *Anaesthesia* 1994; **49**: 819–20

15 Foulkes GD, Robinson JSJ. Intraoperative dexamethasone irrigation in lumbar microdiskectomy. *Clin Orthopaedics Related Res* 1990; **261**: 224–8

16 Ang ET, Goldfarb G, Kohn S, *et al.* Analgésie postopératoire: injection péridurale de phosphate sodique de dexaméthasone. [Postoperative analgesia: epidural injection of dexamethasone sodium phosphate]. *Annales Francaises Anesthesie Reanimation* 1988; **7**: 289–93

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Breath interval as a measure of dynamic opioid effect

J. A. Smart[1], E. J. Pallett[2] and D. J. R. Duthie[1]*

[1]*University Department of Anaesthesia, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK.*
[2]*University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW, UK*
**Corresponding author*

We measured breath interval to characterize the time course of opioid effect in anaesthetized patients breathing spontaneously during knee replacement surgery with concurrent regional nerve blockade. Breath interval was recorded before and after a single dose of fentanyl 0.75 $\mu g\ kg^{-1}$ i.v. Breath interval was measured between the start of successive inspirations, identified by a decrease in carbon dioxide concentration, sampled at the laryngeal mask connection. Nineteen patients were admitted to the study, of whom nine were withdrawn (there was a recording failure for one patient, five patients had inadequate block and three were excessively depressed by the fentanyl). Using MKMODEL software, the mean (SD) dynamic elimination half-life and dynamic mean brain residence time of fentanyl were 15.3 (7.8) and 24.1 (8.1) min, respectively. The times to detection of change from baseline, and peak effect of fentanyl on breath interval were 0.9 (0.6) and 5.2 (1.4) min, respectively. Breath interval increased from 2.9 (1.0) s to a maximum of 9.0 (5.7) s. There were no differences between the time course of changes in breath interval and end-tidal carbon dioxide concentrations. End-tidal carbon dioxide concentrations increased from a baseline of 6.6 (0.9)% to a peak of 8.2 (0.8)%. Breath interval was a useful and reproducible method of monitoring the duration of opioid effect in anaesthetized patients breathing spontaneously when surgical stimulation was not affecting the CNS. The data provide information on the duration of action of fentanyl and could guide dosage.

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The pharmacokinetics of opioid drugs have been reported widely[1] and are relatively straightforward to study by measuring opioid concentrations in serial blood samples after opioid administration. Although such studies provide useful information on the time course of opioid concentrations in the blood, they may not indicate the time course of the pharmacodynamic effects of opioids, because tolerance can develop.

Ideally, to study the duration of action of opioids in human subjects, relief of pain would be used to measure opioid effect. The pharmacodynamic features of the analgesic effect of opioid drugs have been described in animal models using analgesia as a variable. For example, stimulation of the tooth pulp of rabbits has provided information on the duration of analgesia in animals given fentanyl.[2] Other methods used to measure analgesia in human subjects, such as verbal rating scales and visual analogue scales, are imprecise[3] and not applicable to anaesthetized patients. The duration of opioid effect has been studied under anaesthesia[4] by measuring time required for fentanyl supplements during neurolept anaesthesia, based on clinical observations.

In clinical practice, the analgesic effects of pure μ-opioid antagonists have never been separated from their depressant effects on the respiratory system. Although respiratory rate is a poor measure of respiratory function, it offers a method to study opioid effect using the reciprocal, the breath-to-breath interval. Respiratory rate is derived from the reciprocal of breath interval.

Breath interval data may provide information on the duration of action of fentanyl and a guide to dosing interval taken directly from a dynamic effect.

Methods

The study was approved by the Local Ethics Committee, and informed written consent was obtained the day before surgery. Nineteen patients were studied. All were admitted for elective total knee replacement surgery, an operation lasting 45–75 min. Patients were excluded from the study if their weight or any concurrent medical condition made it inappropriate to use the technique of spontaneous breathing through a laryngeal mask airway.

All patients received temazepam 10 mg orally 1 h before

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surgery. Anaesthesia was induced using propofol 2–3 mg kg^{-1} i.v. A laryngeal mask airway was inserted into the pharynx and anaesthesia was maintained with isoflurane 0.8% and nitrous oxide 67% in oxygen.

Sciatic and three-in-one femoral nerve blocks were then performed using a nerve stimulator to guide needle placement. The femoral nerve, lateral cutaneous nerve of the thigh and obturator nerves were all blocked by injecting 0.375% bupivicaine 20 ml next to the femoral nerve. When a current of ≤0.5 mA produced a visible twitch in the quadriceps femoris muscle, pressure was applied just distal to the needle and the bupivicaine was injected. The sciatic nerve was blocked via an anterior approach with 0.375% bupivicaine 20 ml, once a current of ≤0.7 mA produced visible dorsiflexion of the ankle.

After insertion of nerve blocks, patients were transferred into theatre. Routine monitoring of the patient included sidestream analysis of the respiratory gases at the airway opening using a Capnomac Ultima (Datex, Helsinki, Finland). The analogue output of the carbon dioxide concentration was fed to an analogue–digital converter attached to a personal computer. A point on the downstroke of each carbon dioxide waveform was identified from analysis of the area under the curve. The time, in milliseconds, between each of these points was recorded as the breath interval. By digitizing the analogue output of the carbon dioxide monitor to derive the breath interval signal, no further influence on breathing was imposed beyond that used in routine clinical practice.

Approximately 25 min passed between insertion of the peripheral nerve blocks and the start of surgery. This allowed the nerve blocks to achieve their maximal effect before painful surgical stimuli. During this time we measured baseline breath intervals.

After the start of surgery, a further 5 min were used to confirm that surgery was not associated with any alteration in baseline breath interval. Fentanyl 0.75 µg kg^{-1} was then given as a single rapid i.v. injection while each successive breath interval was logged to personal computer.

Patients were withdrawn from the study if their respiratory rate decreased to <6 b.p.m. or if their end-tidal carbon dioxide concentration exceeded 9%.

Analysis

Data obtained throughout the operation were plotted as breath interval against time. A representative example from one patient is given in Figure 1. Fentanyl was injected at time 0. Data points describe a curve resembling curves for blood or plasma concentrations obtained after absorption and elimination of a single dose of drug. We took data points after the peak to represent the elimination phase of opioid from the effect site.

Pharmacokinetic analysis was not attempted. Breath interval provides no value for change in mass of drug; so clearance and volume of distribution cannot be calculated. MKMODEL[5] was used as a convenient means of calculating the rate constant as breath intervals decrease from a maximum back to baseline. It was configured to extrapolate curves to baseline, by dividing the last data point by the elimination rate constant, *k*, and thus to calculate the area under the curve and its first moment to infinity. The slope of the regression line through the latter two-thirds of the natural logarithm of breath intervals from peak to baseline gave *k*. The dynamic elimination half-life ($t_{\frac{1}{2}}$) of the opioid effect was calculated from $t_{\frac{1}{2}}$ ln(2)/*k*. The mean residence time (MRT)[6] of fentanyl in the effect site was also calculated from the ratio of the area under the first moment curve to the area under the curve. Both areas under the curve were extrapolated to zero.

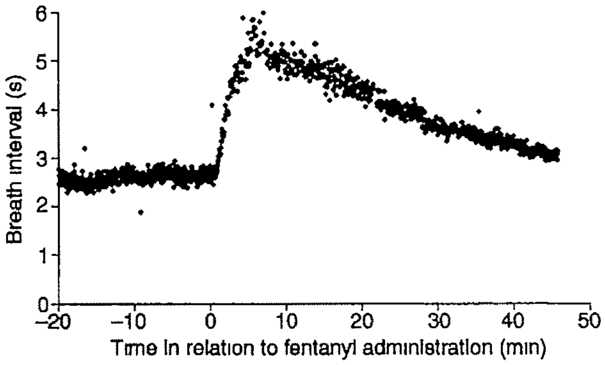

Fig 1 Serial measurements of breath interval before and after fentanyl 40 µg i.v. at time 0. Values before time 0 provide baseline. Breath interval did not return completely to baseline before surgery finished.

Mean and SD are used to describe group values of *k*, $t_{\frac{1}{2}}$ and MRT. Times to onset and peak effect of breath interval and end-tidal carbon dioxide concentration were compared by analysis of variance. Statistical significance was accepted when $P<0.05$.

Results

Nineteen patients were recruited for study. Nine patients were withdrawn from analysis. In one patient, computer logging failed. In three patients, breathing slowed to <6 b.p.m. or end-tidal carbon dioxide concentration increased to >9%, requiring ventilation to be assisted transiently. Five patients had more than usual pain after surgery; they had irregularities in their breath interval curves (Fig. 2) and were considered to have inadequate nerve blocks. The mean (range) age, mean (SD) weight and height of the remaining 10 patients were 61 (27–84) yr, 71 (10) kg and 168 (9) cm. There were seven male patients. Patients received fentanyl 53 (9) µg i.v., equivalent to fentanyl 0.74 (0.12) µg kg^{-1}. The time between induction of anaesthesia and injection of fentanyl was 31 (14) min.

A plot of successive breath intervals against time resembled a plot of blood concentration after absorption of a drug. In such curves, there is a lag before values change from baseline, then values increase rapidly to a maximum and decrease more slowly back to baseline (Fig. 1, Table 1).

The time taken for breath interval to increase from

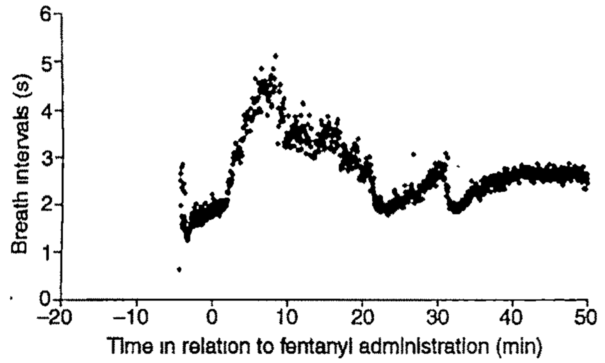

Fig 2 Serial measurements of breath interval before and after fentanyl 75 µg i.v. at time 0 Ineffective femoral three-in-one and sciatic nerve blocks prevented stable baseline breath intervals before i.v. fentanyl. Surgical stimuli affected breath interval during the elimination phase. Data from this patient are not included in analysis of $t_{\frac{1}{2}}$ or MRT.

Table 1. Rate constant of elimination, mean residence time and elimination half-life for breath interval after fentanyl 0.75 µg kg^{-1} i.v.; breath interval and end-tidal carbon dioxide concentrations after fentanyl, together with times from i.v. fentanyl to change from baseline and from i.v. fentanyl to peak values (mean (SD), $n=10$)

	Breath interval	**Carbon dioxide**
Rate constant of elimination (min^{-1})	0.057 (0.030)	
Dynamic elimination half-life (min)	15.3 (7.9)	
Mean residence time (min)	24.1 (8.1)	
Time (min)		
from fentanyl i.v. until change from baseline	0.9 (0.6)	1.3 (1.0)
from fentanyl i.v. to peak effect	5.2 (1.4)	6.7 (1.0)
Baseline value	2.9 (1.0) s	6.6 (0.9)%
Peak value	9.0 (5.7) s	8.3 (0.8)%

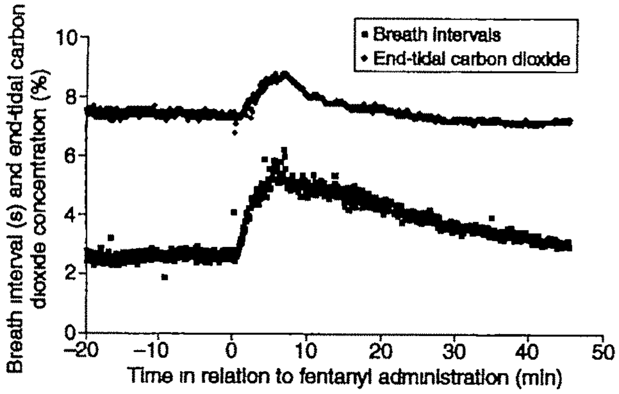

Fig 3 Serial measurements of breath interval(s) (lower trace) and end-tidal carbon dioxide concentration (%) (upper trace) after i.v. fentanyl at time 0

baseline to maximum was the same as that for carbon dioxide (Table 1). The two variables appeared to change simultaneously. Correlation coefficients for the 10 patients between measurements of breath interval and end-tidal carbon dioxide concentrations were 68.6 (23.3)%. When breath interval increased there appeared to be a greater variation in successive breath intervals towards the peak value. No such changes were evident in the end-tidal carbon dioxide plot (Fig. 3).

Discussion

Breath interval was a reproducible method of measuring dynamic opioid effect. We calculated the dynamic MRT and dynamic elimination half-life of fentanyl. Coefficients of variation of these values in the group of 10 patients were 51 and 34%, respectively. These results correspond closely with those from previous reports.[1 2] This method of measuring the duration of opioid effect is easy to perform, non-invasive and does not require the measurement of relief from pain. Analgesic effects of pure µ-opioids in clinical practice have never been separated from respiratory effects; so the time course of changes in breath interval are likely to correspond with changes in analgesic effect.

We calculated the dynamic MRT of fentanyl from the oral absorption model. Although given as a rapid i.v. injection the effect on breath interval is not immediate. This is analogous to the changes in blood concentration seen after oral, subcutaneous or i.m injection where initial absorption must occur. Fentanyl was injected rapidly into a peripheral vein. Circulation to the heart, temporary sequestration in the lung[7] and time taken for uptake from cerebral circulation to the effect site in the brain could delay the onset of effect. However, even with these delays, peak effects were obtained at 8 and 9 min for end-tidal carbon dioxide concentration and breath interval, respectively.

In pharmacokinetic models, MRT equates to the mean duration of the presence of a drug within the body. In our dynamic model, we consider MRT to be the mean duration of drug effect. Breath interval was used as a signal of drug effect. The time to onset of drug effect and time to peak effect were the same for breath interval and end-tidal carbon dioxide concentration. Changes to both occurred in phase, suggesting that they indicate the same drug effect, rather than one responding to a change in the other.

A measurement at each breath was sought to provide data to characterize the rapid onset of effect and recovery of a single i.v. dose of fentanyl in clinical anaesthetic practice. Arterial blood sampling for gas analysis would not have been rapid enough. The ventilatory response to inhaled carbon dioxide is similarly intermittent. The ratio of tidal volume to breath interval measured in minutes would give a value for minute volume at each breath and take account of depth and frequency of ventilation. Tidal volume could have been measured at each breath, but i.v. fentanyl did not influence tidal volume in anaesthetized patients with spinal analgesia undergoing lower body surface surgery. Inspiratory flow was reduced while duration of expiration was increased.[8] End-tidal carbon dioxide concentration is dependent on carbon dioxide production and lung mechanics, and is affected by sampling site, the mode of ventilation, anaesthetic circuit and gas flow, limiting its usefulness as a physiological signal in these study conditions. Breath interval was measured from the carbon dioxide trace because it was easily identified, but it could equally well be measured from chest dimensions or change in direction of flow at airway opening. After a single painful surgical stimulus, breath interval is transiently increased.[9] In the presence of effective nerve blocks, breath interval after i.v. fentanyl showed a smooth transition from baseline to peak, then back to baseline (Fig. 1). With ineffective nerve blocks the breath interval plot became erratic (Fig. 2) and data were impossible to analyse in the manner described. Spinal or epidural anaesthesia could be used more effectively to interrupt transmission of a painful surgical stimulus to the central nervous system. Axial blockade was not available because of its association with increased urine retention: we wanted to avoid catheterization and the consequent risk of bacteraemia.[10]

Anaesthesia was maintained using a volatile anaesthetic agent and a nitrous oxide mixture in oxygen. Both drugs affect the respiratory rate.[11] A change in ventilation caused by fentanyl will affect the uptake and alveolar concentrations of these agents and could affect respiratory timing. However, patients breathed through a laryngeal mask connected to a circle anaesthetic system into which a fresh gas flow delivered nitrous oxide 67% and isoflurane 0.8% in oxygen. Standardizing the concentrations of anaesthetic agents delivered was more practical than attempting to adjust the isoflurane concentration in the fresh gas to achieve a steady-state end-tidal isoflurane concentration.

In summary, breath interval gave a method of calculating the time course of opioid effects. The dynamic opioid half-life obtained can guide the timing of a second dose of opioid in anaesthetized patients, when afferent surgical stimuli are blocked.

References

1 Foley KM. Opioids. *Neurol Clin* 1993; **11**: 503–22
2 Hess R, Herz A, Friedel K. Pharmacokinetics of fentanyl in rabbits in view of the importance for limiting the effect. *J Pharm Exp Ther* 1971; **179**: 474–84
3 Syrjala KL, Chapman CR. Measurement of clinical pain: a review and integration of research findings. In: Benedetti C, Chapman CR, Moricca G, eds. *Recent Advances in the Management of Pain*. New York; Raven Press, 1984: 71–101
4 Holmes CM. Supplementation of general anaesthesia with narcotic analgesics. *Br J Anaesth* 1976; **48**: 907–13
5 Holford N. *MKMODEL*, 5th edn. Cambridge: Biosoft, 1994
6 Cheng H, Gillespie WR, Jusko WJ. Mean residence time concepts for non-linear pharmacokinetic systems. *Biopharmaceut Drug Depos* 1994; **15**: 627–41
7 Boer F, Bovill JG, Burm AGL, Hak A. Effect of ventilation on first-pass pulmonary retention of alfentanil and sufentanil in patients undergoing coronary artery surgery. *Br J Anaesth* 1994; **73**: 458–63
8 Drummond GB. Comparisons of decreases in ventilation caused by enflurane and fentanyl during anaesthesia. *Br J Anaesth* 1983; **55**: 825–35
9 Sutherland RW, Drummond GB. Effects of surgical skin incision on respiration in patients anaesthetised with enflurane. *Br J Anaesth* 1996; **76**: 777–9
10 Williams A, Price N, Willett K. Epidural anaesthesia and urinary dysfunction: the risks in total hip replacement. *J Roy Soc Med* 1996; **88**: 699–701
11 Jonsson LO, Wahlgreen C. Respiratory flow characteristics during isoflurane/nitrous oxide anaesthesia. *Acta Anaesthesiol Scand* 1989; **33**: 331–5

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Comparison of ketamine and morphine for analgesia after tonsillectomy in children†

R. J. Marcus, B. A. Victoria, S. C. Rushman and J. P. Thompson*

University Dept of Anaesthesia and Pain Management, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW, UK

**Corresponding author*

In a double blind study we compared the effects of i.m. ketamine with morphine on postoperative analgesia in children undergoing tonsillectomy. Eighty children (aged 6–15 yr) were randomized to receive either i.m. morphine 0.1–0.15 mg kg^{-1} or ketamine 0.5–0.6 mg kg^{-1}, after induction of a standard general anaesthetic. Pain scores 30 min after extubation were higher ($P<0.05$) in the ketamine group, but were similar thereafter to the morphine group. Mean (SD) times to recovery from anaesthesia were 20.1 (SD 6.5) min in the ketamine group compared to 14.2 (5.6) min in the morphine group ($P<0.01$). There were no differences in supplemental analgesia requirements, or the incidence of vomiting or dreaming between the groups. We conclude that ketamine 0.5 mg kg^{-1} i.m. may be an alternative analgesic for children undergoing tonsillectomy.

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Postoperative pain is common after tonsillectomy; most children require some opiate analgesia, even when paracetamol is given preoperatively.[1] However, opiates may cause respiratory depression, sedation, and nausea and vomiting. Non-steroidal anti-inflammatory drugs (NSAIDs) have been tried with variable results.[1–3] They may cause increased preoperative and postoperative bleeding, and it has been suggested that their use is avoided.[2 3]

Ketamine is a non-competitive antagonist at the *N*-methyl-D-aspartate (NMDA) receptor and has analgesic properties at sub-anaesthetic doses.[4] NMDA receptors in the dorsal horn of the spinal cord are involved in central sensitization to painful stimuli, and 'wind up'. Ketamine has been shown to reduce these effects in humans.[5] It therefore has potential as a perioperative analgesic and may reduce requirements for postoperative analgesia. A previous study showed that ketamine 0.5 mg kg^{-1} given i.v. gave better pain relief than placebo in the first hour after surgery,[6] but there are no studies comparing ketamine with other analgesics in children.

We therefore undertook a double blind, randomized study to compare the effects of ketamine and morphine on postoperative pain after tonsillectomy in children.

Methods

After study approval by the Leicestershire Medical Ethics Committee, 80 children (ASA grades 1 or 2, aged 6–15 yr) admitted as in-patients for elective tonsillectomy or tonsillectomy and grommet insertion were enrolled. Written, informed consent was obtained from a parent or guardian for participation in the study.

Patients with a history of allergy to any of the study drugs were excluded.

Children received topical EMLA cream to facilitate venous cannulation. A standardized general anaesthetic was used. Anaesthesia was induced with thiopental 5–7 mg kg^{-1} or 1–3% halothane and 67% nitrous oxide in oxygen, if venous access could not be obtained. Succinylcholine 1–1.5 mg kg^{-1} was used to facilitate tracheal intubation Anaesthesia was maintained with spontaneous ventilation of 1–2% halothane and 67% nitrous oxide in oxygen. Children were randomized by sealed, numbered envelopes to receive either ketamine 0.5–0.6 mg kg^{-1} or morphine 0.1–0.15 mg kg^{-1} (both drugs being undiluted, and in the smallest possible equivalent volume), administered i.m. into the anterolateral aspect of the thigh after induction of anaesthesia but before the start of surgery. A range of dose for each drug was available to permit accurate titration (to the nearest 0.1 ml) in the lowest possible equivalent volume, on a mg kg^{-1} basis. In almost all cases, the drug dose at the lowest end of the possible range (i.e. ketamine 0.5 mg kg^{-1} or morphine 0.1 mg kg^{-1}) was administered. Tonsil-

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Table 1 CHEOPS pain score (range 4–13)

Cry	No cry	1
	Moan or cry	2
	Scream	3
Facial expression	Smiling	0
	Composed	1
	Grimace	2
Verbal response	Positive	0
	None or other complaints	1
	Pain +/ or other complaints	2
Torso	Neutral	1
	Shifting/tense/shivering/upright/restrained	2
Hands	Not touching wound	1
	Reaching/touching/grabbing wound/restrained	2
Legs	Neutral	1
	Squirm/kicking/drawn up/tensed/restrained/standing/ crouching/kneeling	2

lectomy was performed by dissection and diathermy. At the end of surgery, anaesthesia was discontinued, tracheal extubation performed under deep anaesthesia and the child was transferred to the recovery ward. The anaesthetist, recovery room and ward nurses, and pain score observers were blinded to the identity of the study drug. The time to eye opening to command was noted. Pain was assessed by an independent observer, using both a five-point 'faces' scale (1 =no pain, 5=highest pain score)[7] and the Children's Hospital Eastern Ontario Pain Scale (CHEOPS),[8] (range of scores 4–13) at 30, 60, 120 and 240 min after tracheal extubation (Table 1). Respiratory rate and incidence of nausea and vomiting were also recorded at these times. After 4 h, an enquiry was made as to the occurrence of any dreams or hallucinations. The time to first additional analgesia was also noted. A further dose of morphine 0.1 mg kg^{-1} could be administered in the recovery room if the 'faces' pain score was 5 and the CHEOPS was greater than 11.

Any child receiving rescue analgesia was excluded from the analysis of pain scores. After return to the ward, additional analgesia (diclofenac 1 mg kg^{-1} or paracetamol 15 mg kg^{-1} orally) was available at the request of the child and the discretion of the nursing staff. Parents were asked to complete a questionnaire the morning following surgery, enquiring as to their child's sleep and dreaming overnight and a subjective rating of overall pain relief. Parents of younger children tended to stay with the children overnight and answered questionnaires after direct observation of the children. Parents of older children based their answers on the children's responses.

Power calculations had indicated that 40 children would be required per group to detect a difference of 30% in faces or CHEOPS pain scores with a power of 90% (α=0.05, β=0.1). Data were analysed using Kruskal–Wallis ANOVA and Mann–Whitney *U*-tests for pain scores, *t*-tests for parametric data, or chi-squared for categorical data.

Results

Eighty children were recruited, 40 patients in each treatment group. The groups were similar with respect to age, weight and duration of surgery (Table 2). One child in each group was excluded because of protocol violations. Mean (SD) time to awaken was significantly longer in the ketamine group (P<0.01). Both CHEOPS (Fig. 1) and 'faces' (Fig. 2) pain scores were higher (P<0.05) in the ketamine group 30 min after extubation, but were similar thereafter to the morphine group. There was a preponderance of females in the study as a whole and in the ketamine group, but further analysis showed no significant differences in pain scores

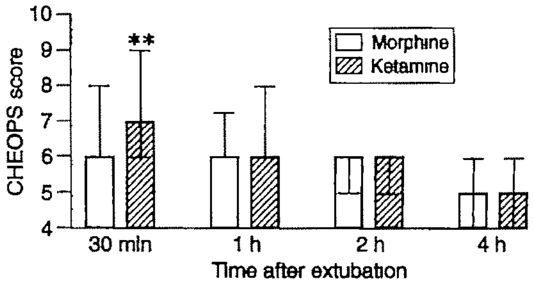

Fig 1 Median (25–75 centile) CHEOPS pain scores at 30 min, 1 h, 2 h and 4 h after extubation Pain scores were higher at 30 min in the ketamine group but were similar thereafter to the morphine group. Median scores at certain time points coincide with values for either the 25th or 75th centile. **P<0.01.

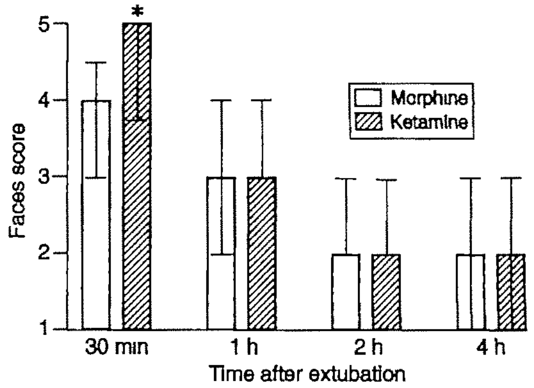

Fig 2 Median (25–75 centile). 'Faces' pain scores at 30 min, 1 h, 2 h and 4 h after extubation Pain scores were higher at 30 min in the ketamine group but were similar thereafter to the morphine group. Median scores at certain time points coincide with values for either the 25th or 75th centile. *P=0.05.

Table 2 Patient characteristics, duration of surgery, postoperative analgesia requirements, and incidence of vomiting and dreaming in the first 4 h after surgery, expressed as mean (SD or range) or number. *P<0.01

Group	Ketamine (n = 39)	Morphine (n = 39)
Age (yr)	10.3 (6–15)	9.8 (6–15)
Weight (kg)	40.3 (16.5)	39.5 (17.2)
Sex (F M)	30 . 10	22 18
Duration of surgery (min)	20.8 (5.0)	21.2 (6.3)
Time to awaken (min)	20.1 (6.6)*	14.2 (5.6)
Rescue morphine required (n)	1	1
Postop analgesia required (n)	34	30
Time to first analgesia (min)	118.9 (60.7)	125.2 (64.3)
Incidence of vomiting (n)	22	19
Incidence of dreaming (n)	3	2

Table 3 Questionnaire results (number) assessing analgesia and sleep patterns during the first postoperative night

Group	Ketamine (n = 32)	Morphine (n = 33)
Good/excellent analgesia	23	20
Slept worse than usual	15	18
Bad dreams	1	2
Good dreams	5	5

between males and females, within or between the groups. One patient in each group required rescue morphine in recovery; the number of children requiring further postoperative analgesia, and mean times to first analgesia were similar. The incidence of vomiting and dreaming during the first 4 h after surgery was similar (Table 2).

Mean (SD) respiratory rates were 20.5 (SD 4.3) min^{-1} and 19.2 (3.8) min^{-1}, 30 min after extubation in the ketamine and morphine groups, respectively, with no significant differences between the groups over the study period. Sixty-five completed questionnaires were returned, 32 from the ketamine group and 33 from those who received morphine. There were no significant differences in sleep patterns or dreams between the groups in the first postoperative night. The numbers who felt pain relief to be good or excellent were also similar (Table 3).

Discussion

This investigation shows that pain scores were higher in the ketamine group at 30 min after extubation, but were similar thereafter to the morphine group. Requirements for additional analgesia and time to first request for analgesia were similar in each group. Only one child in each group required rescue morphine in recovery. Although initial (30 min) postoperative 'faces' pain scores were higher in the ketamine group, a significant proportion (15/38) were too drowsy to perform the scores, and these data may not be representative of the whole group.

The incidence of adverse side effects, such as salivation, dreaming and hallucinations, has been a limiting factor in the use of ketamine in anaesthetic doses (i.e. >2 mg kg^{-1}). In this study, the incidence of bad dreams or hallucinations was low, and was similar in both groups, in accordance with previous data when low-dose ketamine has been used during anaesthesia.[6 9] In a population study, nightmares occurring once or twice weekly were reported in 3.1% of children aged 5–7 yr,[10] but there are very few data documenting the incidence of dreaming in children after anaesthesia. Dreaming is difficult to assess in children, and in the present study a structured postoperative questionnaire was used enquiring as to events during the day of surgery and first postoperative night. Notably, good dreams were reported in five patients in each group. A number of factors may contribute to sleep disturbance or dreaming after surgery, including preoperative anxiety or sleep deprivation, the unfamiliar hospital environment, and the effects of opioids and general anaesthesia. The incidences of good and bad dreams were similar in both groups. This suggests that the effects of low-dose ketamine are relatively unimportant in this context.

We had anticipated that the incidence of vomiting might be reduced in the ketamine group, because of the avoidance of opioids, and vomiting has not been noted as a problem in previous reports using analgesic doses of ketamine.[6 9] However, the incidence of vomiting was ~50%, similar to other studies of children undergoing tonsillectomy where no anti-emetics were given.[11 12] This may reflect the fact that the aetiology of nausea and vomiting is multifactorial in children undergoing tonsillectomy and that routine anti-emetic prophylaxis should be considered.

The apparently long recovery times in both groups may have been related to the design of the study. Patients were extubated under deep halothane anaesthesia and the 'time to awaken' was defined as the time from extubation until the patient was able to open their eyes to command. Variation in the anaesthetic technique could have resulted in a more rapid recovery in both groups. However, recovery was significantly slower in the ketamine group which may be related to its pharmacokinetics. Maximum plasma concentrations occur 20–30 min after ketamine 0.5 mg kg^{-1} in adults, and the elimination half life is 155 min,[13] similar kinetic values to those of i.m. morphine. Maximum plasma concentrations of the active metabolite, norketamine, occur more than 1 h after i.m. ketamine.[13] Ketamine and norketamine have sedative effects, although marked sedation is unlikely at this dose. Alternatively, if intraoperative tachycardia had been associated with ketamine,[4] the inspired halothane concentrations might have been increased in the ketamine group, leading to a delay in recovery. However, these data are not available as intraoperative halothane concentrations were not systematically recorded.

Murray and colleagues[6] showed that ketamine 0.5 mg kg^{-1} provided better analgesia than placebo after tonsillectomy in children. However, they assessed pain relief only in the first hour after surgery and the benefit compared to placebo was small. This is the first study to compare ketamine with morphine, the standard analgesic used for pain relief after tonsillectomy. We did not include a placebo group, as we believe it to be unethical to provide no pain relief after tonsillectomy. Possible limitations of this study relate to the difficulties of pain assessment in children. However, we excluded children under 5 yr as this is the lower age for children to have adequate cognitive and communicative skills for self-reporting measures of pain. Including children having only tonsillectomy (not adenotonsillectomy) to standardize the surgical stimulus also resulted in a higher mean age in our study compared to other studies.[2 3] This is likely to result in more reliable subjective pain scores. We chose to use the 'faces' scale rather than a visual analogue scale (VAS) as younger children may not understand proportionality and therefore may not use a VAS predictably. The use of observer-rated scores also facilitated repeated scoring, particularly in the early postoperative period. The intervals between the 'faces' have not been shown to vary equally, but are rated consistently in order and there is adequate test–retest reliability. However, children may pick the face that they 'like' the best. The CHEOPS[8] is a behavioural scale developed for postoperative pain. Its primary disadvantage is that overt distress behaviour is not necessarily measured as a direct expression of the intensity or quality of the pain experienced. Behavioural scales consistently underscore those children who become quiet and withdrawn with pain. We have used both the faces and CHEOPS pain scales for this study to attempt to cross-validate the results from each, and both did show a similar pattern. Once the child had returned to the ward, provision of additional analgesia was left to the patients' and nurses' discretion. This may have led to unreliability in these data, but as pain scores were low and decreased with time, we were not able to provide a pain score trigger for this.

Ketamine may be a good analgesic for patients undergoing tonsillectomy for obstructive sleep apnoea who may be sensitive to opioids, causing significant respiratory and airway problems. It has been recommended that opioids be used with extreme caution and only short-acting ones should be used if necessary.[14] Ketamine has less effect on airway patency and respiratory drive, and may be an ideal choice in these groups. We have not investigated the use of ketamine in combination with opiates or NSAIDs. It may have a place in low doses as an opiate sparing agent or to improve the initial analgesia provided by NSAIDs. However, the combination of ketamine and an opiate may cause excessive sedation or respiratory depression. Further studies in these areas are warranted.

In summary, although pain scores were higher 30 min after extubation in the ketamine group they were similar thereafter; and there were no differences in numbers requiring, or time of first request for, postoperative analgesia. Ketamine may prove to be a useful alternative to morphine in children undergoing tonsillectomy.

References

1 Rusy LM, Houck CS, Sullivan LJ, Ohlms LA, Jones DT, McGill TJ, Berde CB. A double blind evaluation of ketorolac tromethamine versus acetaminophen in pediatric tonsillectomy: analgesia and bleeding. *Anesth Analg* 1995; **80**: 226–9

2 Gunter JB, Varugheses AM, Harrington JF, Wittkugel EP, Patankar SS, Matar MM, Lowe EE, Myer CM III, Willging JP. Recovery and complications after tonsillectomy in children: a comparison of ketorolac and morphine. *Anesth Analg* 1995; **81**: 1136–41

3 Sutters KA, Levine JD, Dibble S, Savedra M, Miaskowski C. Analgesic efficacy and safety of single-dose intramuscular ketorolac for postoperative pain management in children following tonsillectomy. *Pain* 1995; **61**: 145–53

4 Kochs E, Scharien E, Mollenberg O, Broom B, Schulte am Esch J. Analgesic efficacy of low dose ketamine *Anesthesiology* 1996; **85**: 304–14

5 Arendt-Nielsen L, Pertersen-Felix S, Fischer M, Bak P, Bjerring P, Zbinden AM. The effect of N-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli. a placebo controlled experimental human study. *Anesth Analg* 1995; **81**: 63–8

6 Murray WB, Yankelowitz SM, Le Roux M, Bester HF. Prevention of post-tonsillectomy pain with analgesic doses of ketamine. *South African Med J* 1987; **72**: 839–42

7 Maunuksela E-L, Olkkola KT, Korpela R. Measurement of pain in children with self reporting and behavioral assessment. *Clin Pharmacol Ther* 1987; **42**: 137–41

8 McGrath PA, de Veber LL, Hearn MJ. Multidimensional pain assessment in children. In: Fields HL, Dubner R, Cerveros R, eds. *Advances in Pain and Research Therapy*. New York: Raven Press, 1985; **9**: 387–93

9 Roytblat L, Korotkoruchko A, Katz J, Glazer M, Greemberg L, Fisher A. Postoperative pain: the effect of low dose ketamine in addition to general anesthesia. *Anesth Analg* 1993; **77**: 1161–5

10 Smedje H, Broman J-E, Hetta J. Parents' reports of disturbed sleep in 5–7 year-old Swedish children. *Acta Paediatr* 1999; **88**: 858–65

11 Mather SJ, Peutrell JM. Postoperative morphine requirements, nausea and vomiting following anaesthesia for tonsillectomy. Comparison of intravenous morphine and non-opioid analgesic techniques. *Paediatr Anaesth* 1995; **5**: 185–8

12 Semple D, Russell S, Doyle E, Aldridge LM Comparison of morphine sulphate and codeine phosphate in children undergoing adenotonsillectomy. *Paediatr Anaesth* 1999; **9**: 135–9

13 Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of i.m. and oral ketamine. *Br J Anaesth* 1981; **53**: 805–9

14 Boushra NN. Anaesthetic management of patients with sleep apnoea syndrome. *Can J Anaesth* 1996; **43**: 599–616

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Sedation and general anaesthesia in children undergoing MRI and CT: adverse events and outcomes†

S. Malviya*, T. Voepel-Lewis, O. P. Eldevik, D. T. Rockwell, J. H. Wong and A. R. Tait

Departments of Anesthesiology and Radiology, University of Michigan Health Systems, 1500 E. Medical Center Drive, F3900 Box 0211, Ann Arbor, MI 48109-0211, USA

**Corresponding author*

Quality assurance data were collected prospectively for children who were sedated (n=922) or given general anaesthesia (n=140) for magnetic resonance imaging (MRI) or computerized tomography (CT). The data included patient characteristics, concurrent medication, adequacy of sedation, adverse events and requirement for escalated care. The quality of scans was evaluated. Reasons for preselection of general anaesthesia included previously failed sedation (28%), potential for failed sedation (32%) and perceived medical risk (14%). Hypoxaemia occurred in 2.9% of sedated children, and was more common in children classified as ASA III or IV. Sedation was inadequate for 16% of children and failed in 7%. Failed sedation was associated with greater age (P=0.009), higher ASA status (P=0.04) and use of benzodiazepines as sole sedatives (P<0.03). More of the children who underwent general anaesthesia were ASA III or IV than sedated children, yet the procedure was successful in all the children who underwent general anaesthesia, with one incident of laryngospasm. Excessive motion was noted in 12% of scans of sedated children and 0.7% of those completed with general anaesthesia. We conclude that sedation of children for MRI and CT is associated with risks of hypoxaemia and of inadequate or failed sedation. These adverse events were more likely to occur in older children, those with a higher ASA status and those in whom benzodiazepines had been used as sole sedatives. For a preselected high-risk group of children, general anaesthesia may make MRI and CT scans more successful with minimal adverse events.

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The number of diagnostic and therapeutic procedures done outside of the operating room has increased dramatically in recent years. In children, most of these procedures require sedation, analgesia or both to achieve the degree of cooperation or immobilization necessary to complete these procedures successfully. While most of these procedures themselves pose little risk to the child, the administration of sedation or analgesia may add substantial risk.[1–6] This may be particularly relevant for procedures, such as magnetic resonance imaging (MRI), that could frighten the child, and therefore call for deep sedation. In a previous study, we found that 20.1% of children who were sedated for diagnostic procedures experienced an adverse event.[1] Of greatest concern was the 5.5% incidence of respiratory events; these were more likely to occur in children with an ASA status III or IV. The most frequent adverse event in our study, however, was inadequate sedation (13.1%), which resulted in failure of 3.7% of procedures. We also reported that older children were more likely to experience inadequate sedation and that failed procedures were most likely to occur during MRI and computerized tomography (CT) scanning. Of the children who experienced a failed procedure, some were rescanned following general anaesthesia, while in others the procedure was attempted again with sedation. Early identification of children who may be at risk for adverse events, including failed or inadequate sedation, may make it easier to predict patients for whom general anaesthesia would be safe and efficient and lead to a successful procedure.

In some cases, general anaesthesia may be the only available way of making it possible to scan a child successfully. However, the use of general anaesthesia in these settings has been viewed as costly, impractical and inefficient.[7–9] While recent literature has highlighted the risks of sedation, little information is available about outcomes in children who undergo general anaesthesia before scans. The

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aim of this study was to evaluate outcomes related to sedation and general anaesthesia for CT and MRI. Specifically, we sought to determine the incidence of adverse events, including inadequate or failed sedation, in children undergoing CT and MRI, and to identify risk factors for failed sedation in this sample. We also attempted to discover why primary care practitioners chose general anaesthesia to aid scanning, and to define the incidence of adverse events associated with general anaesthesia in these patients.

Materials and methods

This study was conducted in the MRI and CT diagnostic areas at the University of Michigan Health Care Systems, a tertiary care medical centre. With approval from the Institutional Review Board, all children (from birth to 18 yr) who underwent sedation or general anaesthesia for MRI or CT procedures from January 1997 to January 1998 were included in this observational cohort study. Children who were intubated or ventilator-dependent, or both, and those who were hospitalized before the procedure were excluded from the study.

Sedation

Institutional sedation guidelines based on recommendations by the American Academy of Pediatrics (AAP) were in place at the time of this study.[10] In accordance with these guidelines, sedatives were ordered at the discretion of the child's primary physician. Based on the child's underlying medical history and physical examination, the nurse and radiologist reviewed the appropriateness of orders. Trained paediatric nurses in the diagnostic areas administered all sedatives and monitored the children throughout the procedure under the supervision of the radiologist. Monitoring included continuous pulse oximetry in every case. Arterial pressure was measured before and after the procedure, and more frequently at the discretion of the care-giver. Depth of sedation was assessed at least every 15 min by evaluating response to sound, verbal commands or tactile stimulation. Quality assurance tools[1] were prospectively completed by the nurse responsible for care of the child. Quality assurance data included patient characteristics and ASA physical status, significant medical history and physical examination findings. Procedural data recorded on the quality assurance tool included: medication(s) and their route of administration, time from sedative administration to the start of the procedure, duration of the procedure and time to discharge (i.e. recovery). Children were discharged home when their vital signs had returned to baseline, their level of consciousness was close to baseline and they could maintain a patent airway.

All adverse events were documented on the quality assurance tool in a check-box format as well as with narrative comments. Respiratory events included hypoxaemia (decrease in Sp_{O_2} by $\geqslant 10\%$ of baseline for $\geqslant 30$ s), upper airway obstruction, pulmonary aspiration and respiratory arrest. Oversedation was defined as prolonged sedation (i.e. continuing for >30 min after the procedure had ended) or excessive depth of sedation that resulted in another adverse event or required prolonged monitoring or escalation of care, including admission to the post-anaesthesia care unit, emergency department or inpatient setting. Inadequate sedation was defined as difficulty in completing the procedure because of the child's anxiety or inability to remain still. When the initial dose of sedative was too low to allow completion of the scan, additional doses of the same drug or a second agent were added at the discretion of the nurse and the radiologist after consideration of risk based on the child's underlying medical history. The decision to abort the procedure was made on an individual basis in every case. These sedation failures were documented on the quality assurance tool. Adverse reactions to medications, such as nausea, vomiting or paradoxical reactions, were recorded. For all patients who experienced an adverse event, the following information was recorded: interventions required, patient outcomes related to the adverse event, and escalation of care, i.e. prolonged monitoring or unplanned admission into the hospital.

General anaesthesia

During this study period, quality assurance information was prospectively obtained from all children who underwent general anaesthesia for CT and MRI scans. The decision to use general anaesthesia was made by the primary care physicians, and the reasons for this decision were documented. Decisions were based on guidelines developed by a multidisciplinary committee which recommended an anaesthesiology consultation for children at risk for sedation-related adverse events (such as airway abnormalities and underlying cardiopulmonary disease). Following informed consent, management for children who received general anaesthesia was at the discretion of the attending anaesthesiologist assigned to the care of the child. Care and monitoring were in accordance with mandates from the Joint Commision on Accreditation of Health Care Organizations (JCAHO) and ASA recommendations. Criteria used to determine whether children were ready to be discharged from the post-anaesthesia care unit after general anaesthesia were similar to those for sedation and also included adequate hydration and pain control. Quality assurance data were documented by the anaesthetist and included the same pre-procedure, procedural and recovery information as for sedated children. Adverse event data included airway complications on induction and emergence, hypoxaemia, pulmonary aspiration and respiratory arrest. Cardiovascular events included hypotension, arrhythmia and cardiac arrest. Adverse events and escalation of care as a result of the medication were documented as for sedated children.

The quality of a random sample of MRI and CT scans was evaluated by a radiologist who was blinded to whether general anaesthesia or sedation had been used. These scans were scored using a three-point scale (1, no motion; 2,

Table 1 Reported sedative agents and adverse events Anxiolytic combination. chloral hydrate and benzodiazepine (n=111), or chloral hydrate and benadryl (n=6) Analgesic–anxiolytic combination· chloral hydrate and MS (n=6), or chloral hydrate and meperidine (n=1) The number of adverse events presented in the table is less than the total incidence of adverse events since the medications used were not reported in every case †P=0.004 compared with chloral hydrate as a single agent *P = 0 02 compared with chloral hydrate as a single agent **Mean (SD) doses of chloral hydrate and midazolam were 63 8 (16 7) + 0.1 (0 05) mg kg^{-1} respectively

Sedative (n)	Oxygen desaturation (n=27)	Airway management (n=9)	Inadequate sedation (n=146)	Oversedation (n=4)	Failed procedures (n=65)
Single agents					
Chloral hydrate (679)	21 (3%)	7 (1%)	63 (9%)	4 (<1%)	26 (4%)
mean (SD), mg kg^{-1}	69 (9.9)		62 (16 4)	95 (44 1)	60 1 (15.5)
Benzodiazepine (90)	1 (1%)	0	17 (19%)†	0	8 (9%)*
mean (SD), mg kg^{-1}			0.09 (0 05)		0 099 (0.07)
Barbiturate (2)	0	0	0	0	0
Multiple agents					
Anxiolytic combination (117)	2 (2%)	1 (<1%)	59 (50%)	0	28 (24%)**
Analgesic–anxiolytic combination (7)	1 (14%)	0	1 (14%)	0	0

minor movement; 3, major movement making another scan necessary). The anaesthesia and sedation flowsheets in the medical records of a random sample of patients were reviewed to determine the validity of the quality assurance data.

Statistical analysis

Patient characteristics, medication doses and the incidences of adverse events were analysed using descriptive statistics and are presented as percentages or means (SD) where appropriate. The relationships between non-parametric variables such as ASA status and incidence of adverse events were studied using chi-squared analysis or Fisher's exact tests as appropriate. Continuous data, such as age, were compared using unpaired t-tests. For all comparisons, P values of ≤ 0.05 were considered statistically significant. Factors found to be significant by univariate analysis were entered into logistic regression models to determine their contribution to inadequate or failed sedation and to respiratory events.

Results

Nine hundred and twenty-two children (aged 4 (birth–18) yr; 53% male and 47% female) received sedation for CT (n=392) and MRI (n=530) during the study period. Fifty-three per cent were classified as ASA I, 39% as ASA II and 8% as ASA III or IV. Two-hundred and three children (22%) experienced an adverse event related to sedation, but all events were appropriately managed and the diagnostic procedure was successfully completed in 93% of cases. The description of sedative agents used and adverse events is presented in Table 1.

Twenty-seven children (2.9%) experienced oxygen desaturation. Of these, 21 had been given chloral hydrate as the sole sedative (28–78 mg kg^{-1}), two had received chloral hydrate and midazolam, one midazolam alone, and one chloral hydrate and morphine. In two cases, the medication(s) used were not recorded. In each case, the child returned to baseline saturation with interventions that included: supplemental oxygen (n=17), repositioning of the airway (n=2) or both (n=7). One child returned to baseline saturation without any intervention. The respiratory event necessitated prolonged monitoring/observation at the diagnostic site in two cases, and in the emergency department or the post-anaesthesia care unit in another two cases. One child was admitted overnight because of a continued requirement for supplementary oxygen. Four procedures were aborted as a result of the respiratory event, three of which were rescheduled to be done under general anaesthesia. Interestingly, 7% of children classified as ASA III or IV experienced oxygen desaturation, compared with only 3% of those classified as ASA I or II (P=0.03). However, a logistic regression model failed to find any variable that was predictive of respiratory events.

Sedation was deemed inadequate for 146 children (50/392 CT (13%); 96/530 MRI (18%)). One hundred and twenty-three (84%) of these children had received chloral hydrate as the initial sedative. Intravenous midazolam was added in an effort to complete the procedure in 59 (40%) children and morphine was added in one case. Seventeen children who were inadequately sedated had received intravenous midazolam as the sole sedative. In six cases the medication(s) used was not recorded. Children in whom sedation was deemed inadequate were older than those with adequate sedation (4.9 (0.014–17.9) and 3.7 (birth–18.4) yr, respectively; P=0.001). Sedation was inadequate more commonly for children classified as ASA III–IV than for those classified as ASA I–II (24% and 15%, respectively; P=0.04). Sixty-four procedures were aborted as a result of failed sedation (13/392 CT (3.3%); 51/530 MRI (9.6%)). Of these, 11 (17%) were rescheduled to be done with sedation and 41 (64%) with general anaesthesia. For the remaining 12, it was not reported what course would follow. The interval between failed and rescheduled scans ranged from 2 to 77 days. Children whose sedation failed were older than those with successful procedures (5.1 (0.05–17.9) and 3.8 (birth–18.4) yr, respectively; P=0.009). The ASA status of children whose sedation failed was not significantly different from that of children with successful procedures (10.3% ASA III–IV and 7.8% ASA I–II). Age and ASA physical status were entered into a logistic regression model to determine their value as predictors of inadequate or failed sedation. Of these factors, age was the only variable predictive of inadequate sedation ($P=0.0005$) and of failed sedation ($P=0.004$).

Thirty-four children experienced medication-related adverse events, which included: nausea and vomiting ($n=12$), paradoxical reaction ($n=19$), inadvertent drug overdose ($n=2$) and drug-related rash ($n=1$). Of the children who received the drug overdose (chloral hydrate 160 mg kg^{-1} in both cases), one required prolonged monitoring in the post-anaesthesia care unit and the other in the diagnostic area. Neither of these children experienced respiratory problems.

During the study period, 140 children (aged 4.6 (0.083–15.9) yr; 54% male and 46% female) underwent general anaesthesia for CT ($n=25$; 18%), MRI ($n=112$; 80%) or both procedures ($n=3$; 2%). Of these, 39 (28%) required general anaesthesia as a result of a previously failed sedation. Twenty-six (18%) children were selected to have general anaesthesia because the primary physician thought that the child would be unable to cooperate and 18 (13%) because the procedure was expected to be lengthy. In addition, 19 (14%) children had an underlying medical condition (e.g. sleep apnoea, difficult airway, multiple allergies) that may have made sedation riskier. In 38 (27%) cases, the reason for selecting general anaesthesia was unclear. Given these selection criteria, more children who underwent general anaesthesia were classified as ASA III–IV than those who received sedation during this same period (18% compared with 8%; $P=0.0006$). A significantly greater proportion of children who required general anaesthesia underwent an MRI scan compared with those who were sedated (82% and 57%, respectively; $P<0.0001$).

At the discretion of the responsible anaesthesiologist, general anaesthesia was induced via the inhaled route using halothane or intravenously using propofol or thiopental and maintained with isoflurane with or without nitrous oxide. Patients were allowed to breathe spontaneously via a laryngeal mask airway or endotracheal tube, or were placed on a ventilator depending on their medical history. One child in this sample experienced laryngospasm and oxygen desaturation on the way to the post-anaesthesia care unit. This child was given succinylcholine and required bag and mask ventilation, but subsequently recovered uneventfully. One other child with a history of an underlying seizure disorder had a seizure on emergence that resolved without intervention.

Table 2 shows the time taken to induce sedation or general anaesthesia and the durations of the procedure and the recovery period. The time to onset of procedure was significantly longer in children who were inadequately sedated than in those who had been sedated successfully (52 (26) and 37 (17) min, respectively; $P<0.0001$). Children who experienced failed sedation took longer to recover than those whose procedures were completed successfully (40 (21) and 24 (19) min, respectively; $P<0.0001$). The quality of 165 diagnostic images was reviewed and demonstrated that general anaesthesia resulted in less motion artefact than sedation (Table 3).

A random sample of medical records ($n=65$) was selected to evaluate the reliability of the quality assurance data. Only one (1.5%) of these 65 medical records indicated a respiratory event that was not reported on the quality assurance tool. One sedation record indicated that nausea and vomiting occurred after the child had been given chloral hydrate with his oatmeal. The remaining records were consistent with the quality assurance documentation and reported adverse events in 24 cases.

Discussion

MRI and CT procedures themselves pose little risk to children, but sedation or general anaesthesia–when used to facilitate these procedures–may add substantial risk. Indeed, the present study found a 2.9% incidence of hypoxaemia and a failure rate of 7% in children who received sedation for these procedures. In contrast, the procedure was successful in all of the children who received general anaesthesia during the study period, with one incident (0.7%) of laryngospasm, despite the higher risk characteristics of these children. In all children, adverse events were promptly recognized and managed appropriately, resulting in no long-term sequelae. These findings probably reflect the impact of recent changes in sedation practices based on AAP guidelines[10] and regulatory agency (i.e. JCAHO) mandates.[11]

Previous investigators have highlighted the risk of life-threatening adverse events related to sedation of children for diagnostic and therapeutic procedures.[2–6 12 13] Of greatest concern is the risk of respiratory depression and hypoxaemia that may have potentially long-term consequences. One previous study found an 89% incidence of oxygen desaturation in children who were sedated for gastrointestinal endoscopy.[14] In the present study, we found a relatively low incidence of oxygen desaturation (2.9%). Similar to previous reports, respiratory events were more likely to occur in children with an ASA status III or IV than in those of ASA I or II.[1 15 16] The low incidence of respiratory events in our sample may, in part, be explained by the fact that only 8% of children with ASA III or IV underwent sedation. These findings support the recommendations of the AAP that children with ASA III–IV require additional and individual consideration. While the incidence of these events was low, the majority required intervention (airway management in nine cases) and four procedures had to be aborted as a result of the event; three of these were rescheduled to be done with general anaesthesia. No respiratory event resulted in long-term sequelae, probably because of appropriate monitoring and early intervention in all cases. Despite the low incidence of respiratory events, their life-threatening nature underscores the importance of personnel trained in airway management being present. This recommendation is supported by Sury and colleagues who reported a <1% incidence of oxygen desaturation in 1155 children who were sedated for MRI by nurses trained in sedation and airway management.[17]

Table 2 Duration (in minutes) of procedure and recovery times in the two groups (mean (SD))

Time period	Sedation group		General anaesthesia group	
	MRI	CT	MRI	CT
Procedure onset time	42.4 (19.7)	36 (18.4)	23.1 (11.5)	19.4 (12.6)
Duration of procedure	47 (26.1)	17.4 (11.3)	82.5 (43.3)	54.4 (44.9)
Recovery time	28.8 (18.8)	19.5 (21.2)	70 (34.1)	59.9 (36.9)

Table 3 Quality of MRI and CT scans in the sedation and general anaesthesia groups (*n* (%))

	Sedation group ($n = 80$)		General anaesthesia group ($n = 85$)	
	MRI ($n = 60$)	CT ($n = 20$)	MRI ($n = 67$)	CT ($n = 18$)
No motion	40 (67)	17 (85)	56 (84)	18 (100)
Little motion	13 (22)	3 (15)	10 (15)	0
Motion requiring repeated scan	7 (12)	0	1 (1)	0

Although not life-threatening, inadequate sedation remains a significant clinical problem. This outcome can be costly in terms of quality of the scan, increased personnel time, variability in onset of sedative action resulting in downtime of the scanner, lost revenue from failed procedures, and inconvenience to patients and families. Indeed, we found that the quality of scans was not optimal in 29% of sedated cases. Furthermore, the time from administration of sedatives to initiation of procedure was significantly longer in children who experienced inadequate sedation. Inadequate sedation led to 63 failed procedures which, if successful, would have been billed at approximately \$1200 h^{-1}. These failures, therefore, resulted in a significant loss of revenue to the institution. Several of these failed procedures were rescheduled with sedation or general anaesthesia, compounding the charges to the institution and third-party payers. Lastly, the costs to patients and families in terms of travel time, repeated trips to the hospital, lost work time and, perhaps most importantly, delayed diagnosis are immeasurable. It is therefore important to identify those at risk for inadequate or failed sedation to permit use of alternative techniques of sedation or even general anaesthesia if necessary.

As we and other investigators have reported previously,[1 18] sedation was more likely to be inadequate or fail in older children. In our sample, the majority of children received a single sedative agent for their scan; this produced adequate sedation in 90% of cases. However, 5% of all cases for which a single drug was used were aborted because of inadequate sedation. Of the children with failed sedation who received chloral hydrate as a sole agent, all had received a dose within the recommended range (50–90 mg kg^{-1}, maximum 2000 mg). Interestingly, a previous study has suggested that the dose of chloral hydrate should be based on age, resulting in larger doses for older children.[19] It is unclear whether such a dosage adjustment would have reduced the incidence of failed sedation in our sample. Compared with chloral hydrate, when a benzodiazepine was used alone, sedation was more likely to be inadequate and to result in a failed procedure. In some cases, a second drug was not added, presumably because of a perceived increased risk. Indeed, previous investigators have reported a greater risk of sedation-related adverse events when multiple sedatives were used.[3 12] We also found that sedation was more often inadequate in children with ASA status III or IV than in those with ASA I or II. This may reflect a reluctance to administer larger doses or multiple sedative drugs to these patients perceived to be at increased risk related to sedation. Variability in response to the initial sedative agent may require titration of a second agent to the desired effect in some instances. Of the children in our sample who received a second sedative agent in an attempt to complete the scan, 77% were scanned successfully. The incidence of respiratory and other adverse events was no different with the use of single or multiple agents. These data suggest that, in selected children, addition of a second drug may aid the completion of scans without increasing risk.

The use of general anaesthesia to aid diagnostic and therapeutic procedures has been viewed as costly, associated with high risk and inefficient.[7–9] Indeed, Squires and colleagues reported that general anaesthesia added \$1200 to the cost of gastrointestinal endoscopic procedures.[9] During our study period, general anaesthesia was used to aid MRI and CT scans in 140 children. In the majority of these cases, the primary physician had chosen general anaesthesia as the initial intervention because of the potential for a failed procedure or a perceived increased risk of adverse events resulting from underlying conditions such as congenital heart defects or airway abnormalities. The children who received general anaesthesia were, therefore, a higher risk group than those who received sedation as evidenced by their higher ASA status. Yet these children experienced few adverse events from general anaesthesia. Of greatest concern was the incident of laryngospasm that occurred on the way to the post-anaesthesia care unit. Prompt recognition and aggressive intervention averted potential long-term consequences of this event which underscores the need for continued monitoring of all children who receive general anaesthesia even during transport. Furthermore, depending on the location of the procedure, it may be prudent to allow these patients to recover at the diagnostic site before transport.

We were unable to make direct comparisons between children who received sedation and those who received general anaesthesia since it was not possible to randomize children to either group. Children who underwent general anaesthesia were preselected, based upon high risk in some cases and expected duration of the procedure in others, and, as a result, statistical comparisons between groups would have been inappropriate. In general, however, general anaesthesia appeared to be more efficient in terms of time to onset of the procedure, but resulted in a longer duration of recovery in the hospital. The increased costs associated with administration of general anaesthesia may, therefore, include added costs related to recovery. Although general anaesthesia may cost more to administer than sedation, in our patients it helped scans to be completed with negligible movement and a low incidence of adverse events. The costs of general anaesthesia for a selected high-risk group of patients may be offset to some extent by the increased costs related to failed procedures.

One limitation of this study is related to the self-report bias inherent in the method of data collection. To minimize this bias, we reviewed a random sample of medical records in each group. Not surprisingly, we found <100% compliance with the required documentation and with institutional sedation guidelines. Of the records available for review, only one had a documented respiratory event that was not reported on the quality assurance tool, and one reported non-compliance with institutional nil-by-mouth guidelines for sedated patients. While this review supports the reliability of our data, we emphasize that the incidence of adverse events reported here was probably lower than the true incidence of adverse events from sedation and general anaesthesia.

Our data demonstrate that sedation of children for MRI and CT is associated with risks of hypoxaemia, inadequate sedation and failed sedation, and support the use of stringent guidelines to enhance the safety of sedated children. A higher ASA status was significantly related to the incidence of hypoxaemia and inadequate sedation. Greater age and the use of benzodiazepines as sole sedatives were associated with a higher incidence of failed sedation. These data support the need for careful selection of appropriate candidates for sedation and additional and individual consideration for children with a high ASA status. Furthermore, our data suggest that general anaesthesia is a safe alternative to facilitate MRI and CT scans in children perceived to be at increased risk for sedation-related adverse events or for those with a history of failed sedation.

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References

1 Malviya S, Voepel-Lewis T, Tait AR. Adverse events and risk factors associated with the sedation of children by non-anesthesiologists. *Anesth Analg* 1997; **85**: 1207–13

2 Coté CJ, Alderfer RJ, Notterman DA, Fanta KB. Sedation disasters: adverse drug reports in pediatrics–FDA, USP, and others. *Anesthesiology* 1995; **83**: A1183

3 Jastak JT, Peskin RM. Major morbidity or mortality from office anesthetic procedures: a closed-claim analysis of 13 cases. *Anesth Prog* 1991; **38**: 39–44

4 Strain JD, Campbell JB, Harvey LA, Foley LC. IV. Nembutal: safe sedation for children undergoing CT. *Am J Roentgenol* 1988; **151**: 975–9

5 Jastak JT, Pallasch T. Death after chloral hydrate sedation: report of case. *J Am Dent Assoc* 1988; **116**: 345–8

6 Granoff DM, McDaniel DB, Borkowf SP. Cardiorespiratory arrest following aspiration of chloral hydrate. *Amer J Dis Child* 1971; **122**: 170–1

7 Wilson C. Who should perform pediatric endoscopic sedation? *J Pediatr Gastroenterol Nutr* 1994; **18**: 114

8 Coté, CJ. Monitoring guidelines: do they make a difference? *Am J Roentgenol* 1995; **165**: 910–12

9 Squires RH, Morriss F, Schluterman S, Drews B, Galyen L, Brown K. Efficacy, safety, and cost of intravenous sedation versus general anesthesia in children undergoing endoscopic procedures. *Gastrointest Endosc* 1995; **41**: 99–104

10 Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. *Pediatrics* 1992; **89**: 1110–15

11 JCAHO. *Comprehensive Accreditation Manual for Hospitals. The Official Handbook.* Oakbrook Terrace, IL: Joint Commision on Accreditation of Health Care Organizations, 1997

12 Yaster M, Nichols D, Deshpande J, Wetzel R. Midazolam–fentanyl intravenous sedation in children: case report of respiratory arrest. *Pediatrics* 1990; **86**: 463–7

13 Greenberg SB, Faerber EN, Aspinall CL. High dose chloral hydrate sedation for children undergoing CT. *J Comput Assist Tomogr* 1991; **15**: 467–9

14 Dubreuil M, Da Conçeicao M, Lamireau T, Meymat Y, Bidalier I. Oxygen desaturation in children during gastro-intestinal endoscopy: general anesthesia versus sedation. *Anesthesiology* 1995; **83**: A1184

15 Vade A, Sukhani R, Dolenga M, Habisohn-Schuck C. Chloral hydrate sedation of children undergoing CT and MR imaging: safety as judged by American Academy of Pediatrics guidelines. *Am J Roentgenol* 1995; **165**: 905–9

16 Gilger MA, Jeiven SD, Barrish JO, McCarroll LR. Oxygen desaturation and cardiac arrhythmias in children during esophagogastroduodenoscopy using conscious sedation. *Gastrointest Endosc* 1993; **39**: 392–5

17 Sury MRJ, Hatch DJ, Deeley T, Dicks-Mireaux C, Chong WK. Development of a nurse-led sedation service for paediatric magnetic resonance imaging. *Lancet* 1999; **353**: 1667–71

18 Ronchera-Oms CL, Casillas C, Marti-Bonmati L *et al.* Oral chloral hydrate provides effective and safe sedation in pediatric magnetic resonance imaging. *J Clin Pharmacol Ther* 1994; **19**: 239–43

19 Marti-Bonmati L, Ronchera-Oms CL, Casillas C, Poyatos C, Torrijo C, Jimenez NV. Randomized double-blind clinical trial of intermediate- versus high-dose chloral hydrate for neuroimaging of children. *Neuroradiology* 1995; **37**: 687–91

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Fentanyl and midazolam anaesthesia for coronary bypass surgery: a clinical study of bispectral electroencephalogram analysis, drug concentrations and recall

G. Barr[1], R. E. Anderson[1], S. Samuelsson[1], A. Öwall[1] and J. G. Jakobsson[1 2]*

[1]*Department of Cardiothoracic Anaesthetics and Intensive Care, Karolinska Hospital, Stockholm, Sweden.*
[2]*Department of Anaesthetics, Sabbatsbergs Hospital, Stockholm, Sweden*

**Corresponding author: Department of Cardiothoracic Anaesthetics and Intensive Care, Karolinska Hospital, S-171 76 Stockholm, Sweden*

Bispectral index (BIS) was assessed as a monitor of depth of anaesthesia during fentanyl and midazolam anaesthesia for coronary bypass surgery. In 10 patients given morphine premedication, anaesthesia was induced with a combination of midazolam and fentanyl and thereafter maintained with a continuous infusion of a mixture of midazolam and fentanyl 5 and 50 µg kg^{-1} h^{-1}, respectively. BIS was recorded continuously but not shown to the attending anaesthetist. Plasma concentrations of midazolam and fentanyl were measured five times during the procedure. An auditory stimulus was given during bypass. All patients were interviewed twice after operation for explicit and implicit recall. No patient had any anaesthetic complications. BIS decreased during anaesthesia, but varied considerably during surgery (range 36–91) with eight patients having values >60. Midazolam and fentanyl drug concentrations did not correlate with BIS. No patient reported explicit or implicit recall. During clinically adequate anaesthesia with midazolam and fentanyl BIS varies considerably. The most likely reason is that BIS is not an accurate measure of the depth of anaesthesia when using this combination of agents.

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Patients about to undergo general anaesthesia may fear that they will be aware of the operation and be able to remember it afterwards. Awareness with recall is rare, though, occurring in about 0.2% of patients undergoing anaesthesia for general surgery.[1] A greater incidence, >1%, has been reported during cardiac surgery.[2]

The bispectral index (BIS), derived from bispectral analysis of the electroencephalogram, has recently been introduced to monitor the depth of anaesthesia. Ideally such a monitor should measure the depth of anaesthesia irrespective of the anaesthetic agent(s) used or the type of surgical procedure. We investigated the clinical value of BIS during fentanyl and midazolam anaesthesia for coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB). A standardized auditory stimulus was presented at predetermined times during CPB and patients were interviewed for explicit and implicit recall. Plasma concentrations of fentanyl and midazolam were measured.

Methods

Ten patients with a mean age of 69 yr (range 50–83 yr) and scheduled for elective CABG surgery were studied after approval from the hospital ethical committee and informed consent. All patients were seen the day before surgery and informed about the study and its objectives. They were told that a sound (not specified in detail) would be presented during anaesthesia that they would later be asked to recall. About an hour after intramuscular premedication with morphine 5–15 mg, anaesthesia was induced with midazolam 0.05 (0.03–0.12) mg kg^{-1} and fentanyl 10 (7–12) μg^{-1}. Pancuronium 0.1 mg^{-1} was given as a muscle relaxant to facilitate endotracheal intubation A continuous infusion of fentanyl and midazolam was started (5 and 50 µg kg^{-1} h^{-1}, respectively) and maintained until completion of surgery; supplementary doses of fentanyl or midazolam were given at the discretion of the anaesthetist

Standard procedures were used for CPB. Core temperature was reduced or was allowed to drift to 34°C. An auditory stimulus (100 dB, duration 60 s) was presented five times during CPB. BIS (Aspect Medical Systems; version 3.12, Natick, MA, USA) was measured continuously; the attending anaesthesiologist was not shown the output values.

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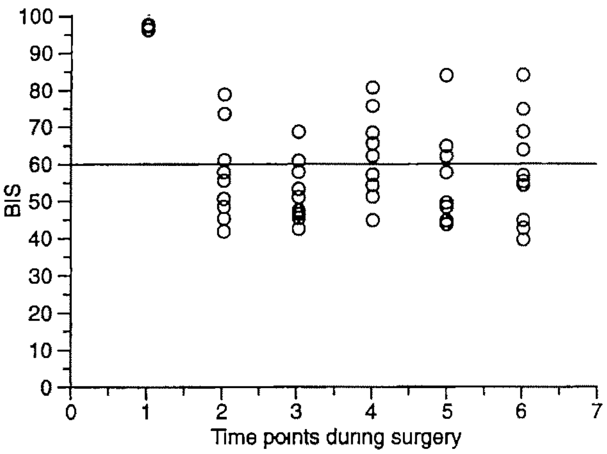

Fig 1 Bispectral index at various times during coronary bypass surgery (n=10). 1, before induction; 2, sternotomy, 3, heparin; 4, start of bypass; 5, end of bypass; 6, skin closure

Table 1 Plasma drug concentrations (median (range)) and bispectral index (BIS) during bypass surgery (n=10)

Time during procedure	Midazolam (ng ml^{-1})	Fentanyl (ng ml^{-1})	BIS (no. of patients)		
			<60	>60	>75
Before induction	0	0	0	10	10
Sternotomy	78 (49–133)	5.0 (3.7–7.8)	6	4	0
Heparin	102 (52–158)	6.4 (3.4–11.9)	7	3	1
Start of bypass	90 (54–113)	4.8 (2.8–7.8)	5	5	2
End of bypass	94 (55–145)	4.9 (3.0–6.6)	7	3	1
End of surgery	103 (87–122)	5.2 (3.2–10.2)	6	4	1

Blood samples were drawn from the radial artery catheter before induction, at sternotomy, when heparin was given, at the start, middle and end of CPB, and at skin closure. Samples were stored in a freezer for blinded, batch analysis.

Patients were interviewed on each of the first 2 days after the operation using a fixed predefined questionnaire. At the first interview they were asked to describe their experience of anaesthesia. At the second meeting the patients were also asked specifically about recall of any special sound. They were given a number of associative proposals. If there was still no recall, the actual sound was presented and the patients were asked again for recollections from the surgical procedure.

Results

The 10 patients studied had mean (SD) body weight of 78 (13) kg. All patients had an uncomplicated surgical course, with a mean surgical time 158 (19) min and mean anaesthesia time 198 (35) min. Haemodynamic measurements were stable.

All patients were awake and fully oriented at arrival in the operating theatre and at induction BIS was between 96 and 99. BIS decreased in all patients with induction, but during surgery it varied between 36 and 91. Almost 40% of BIS values at the time of blood sampling were >60 (Table 1, Fig. 3).

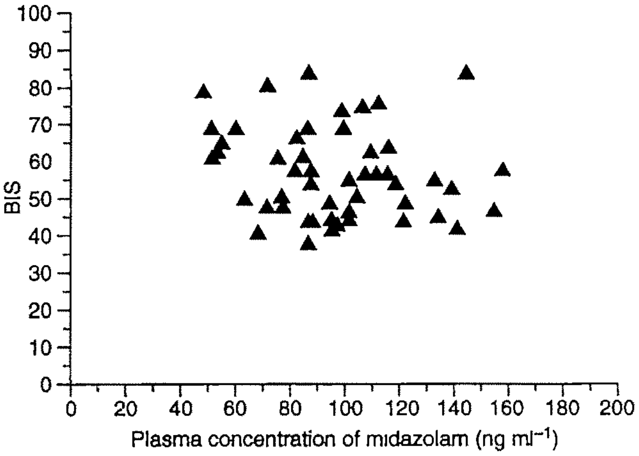

Fig 2 Bispectral index plotted against midazolam plasma concentration (ng ml^{-1}) during bypass surgery (n=10).

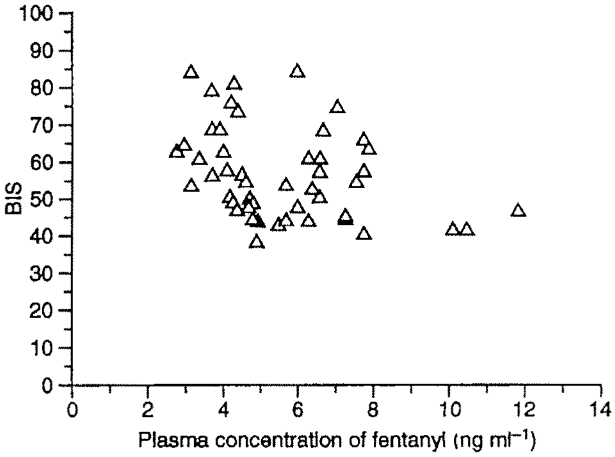

Fig 3 Bispectral index plotted against fentanyl plasma concentration (ng ml^{-1}) during bypass surgery (n=10).

Only two of the 10 patients studied did not have BIS values or >60 at some point during surgery. The BIS values in each subject during anaesthesia varied, with a range that was as small as 15 or as large as 50 (median range was 30).

No drug accumulation occurred. The median plasma concentrations of fentanyl and midazolam did not change during anaesthesia (Table 1). Plasma drug concentrations varied widely between individuals. BIS did not correlate with fentanyl (r^2=0.13) or midazolam plasma concentration (r^2=0.034; Figs 2 and 3). In individual patients, there was no correlation between drug plasma concentration changes and BIS.

No patients reported explicit recall of intraoperative events at interview on the first or second day after operation. No patient could recall the acoustic stimulus presented repeatedly during CPB, either after given strong associations or when actually hearing it.

Discussion

General anaesthesia is a state of pharmacologically induced depression of the central nervous system causing unconsciousness. Anaesthesia is not an on–off phenomenon but a continuum, a gradual depression of cognitive and autonomic functions. Most anaesthetics cause a dose-dependent increase in anaesthetic depth. Many hypnotics and anaesthetics also cause varying degrees of amnesia.[3] Recollection of a stimulus requires an initial activation of the sensory system, central processing of the information and, finally, retrieval of information. The memory process can be separated into explicit or conscious learning and implicit or unconscious retrieval of information.

Awareness with explicit recall of intraoperative events is a feared complication of general anaesthesia with potentially serious adverse psychological sequelae.[4] The incidence of explicit awareness with recall after general anaesthesia is, however, small: about two per thousand patients.[1] Implicit processing has been shown to be less affected by general anaesthesia than explicit memory processing and may continue subconsciously during clinically adequate anaesthesia.[5] Implicit intraoperative awareness and postoperative recall of auditory stimuli have been reported in up to half of patients undergoing cardiac surgery with opiate and benzodiazepine anaesthesia.[6 7]

Most studies of recall suggest that hearing is one of the most receptive sensory channels for perception during general anaesthesia.[8 9] Although explicit recall, especially of pain and paralysis, is a serious complication, adjusting anaesthetic depth to preserve implicit processing of auditory information could be useful. Several studies suggest new therapeutic possibilities with implicit processing[10] that would need carefully titrated depth of anaesthesia however this places additional demands on monitoring.

The ideal monitor of depth of anaesthesia should be able to measure accurately different degrees of anaesthetic depth, such as the transition from wakefulness to unconsciouness, loss of explicit as well as implicit memory processing, loss of motor response to surgical stimulation and loss of autonomic response. Furthermore, all common anaesthetics should be comparable on the same scale. Bispectral analysis of the electroencephalogram can estimate the hypnotic effects of propofol and halogenated agents. BIS has been proposed to be a useful monitor during cardiac surgery with CPB[11] when the usual haemodynamic responses and signs such as sweating or tear production are less dependable markers of anaesthetic depth. In addition, the requirement for early extubation in some patients would make such a monitor useful to avoid excessive anaesthesia. BIS may also be useful in determining the degree of sedation in intensive care patients.[12]

Anaesthesia for coronary surgery is frequently based on a combination of a large dose of an opioid with a hypnotic or a volatile agent. In this study a combination of fentanyl and midazolam was used and anaesthesia was adjusted according to clinical needs at the discretion of the anaesthesiologist. Midazolam and fentanyl have a synergic effect on cognitive depression. In studies of the interactions between fentanyl and sevoflurane, and fentanyl and propofol, a maximum effect for fentanyl occurs at a plasma level of about 3–4 ng ml^{-1}.[13–15] The plasma concentrations in the present study were greater than this, but with large differences between patients, and considerably less than those found in the study by van der Maaten and colleagues of patients having cardiac surgery.[16] The large variation in plasma concentrations we found supports the observations of van der Maaten and colleagues who also found a two to threefold variation when using midazolam and an opioid.[16] The midazolam and fentanyl concentrations throughout the procedure did not differ from their initial values, demonstrating that the continuous drug infusion technique provides unchanged drug concentrations during CPB and that no drug accumulation occurs during the procedure.

The considerable variation in BIS observed here is, in some respects, similar to that found during sedation of intensive care patients.[12] In our study BIS not only varied considerably but was, in general, surprisingly large. Such values are associated with a great likelihood of awareness and the capability to follow command.[17 18] A BIS value of <60 is often regarded as the criterion for adequate anaesthesia, while a value of >70 is frequently seen during awakening.[18] Several factors may have led to the observed variation in BIS. Hypothermia may have affected the BIS measurements during bypass, as discussed by Doi and colleagues.[19] Cardiac surgery with profound hypothermia affects electroencephalographic recordings because of changes in conductance,[19] but our patients were operated on at 34°C and gave no problems with recording apart from during diathermy. Furthermore, the variability was present both before and after the bypass period. The variability may, of course, be explained by inadequate depth of anaesthesia. Although we detected no apparent awareness during surgery, and although haemodynamic measurments were stable, muscle relaxants, beta-blocking drugs and blood volume changes could have masked many of these clincial indicators of adequate anaesthesia. No patient reported recall when actively interviewed on two occasions after operation, even though auditory stimuli are resistant to suppresion by fentanyl and midazolam anaesthesia. No consistent decrease in BIS was found with increasing plasma concentrations of either drug. The most plausible explanation for the high BIS values seems to be that BIS reflects anaesthetic depth less accurately when fentanyl and midazolam are used as anaesthetics. We have shown in a previous study that increasing concentrations of nitrous oxide have no effect on BIS,[20] and addition of fentanyl to propofol anaesthesia causes large BIS values.[21 22] The weak correlation between decreasing BIS and an increasing fentanyl concentration supports results obtained in volunteers.[17]

As discussed above, no patient recalled events during the operation. The timing of, and technique for, evaluating awareness and recall have considerable impact on the results.[1] The lack of any explicit recall in this study with so few patients is not surprising, as explicit recall is infrequent.[1] The lack of implicit recall of the auditory stimulation during surgery, which should be detectable even in the small number of patients in this study, confirms the adequacy of the anaesthetic depth. Technique and time of stimulation are important for implicit memory testing.[23]

In conclusion, this study has shown that although anaesthetic depth was adequate and no recall was reported, BIS varied widely and values that are usually related to excessively light anaesthesia or wakefulness were occasionally observed. BIS did not correlate with midazolam and fentanyl plasma concentrations. A measurement such as BIS should, ideally, be suitable for determining the depth of anaesthesia for all anaesthetics on a common scale. For coronary surgery with fentanyl and midazolam anaesthesia, the BIS algorithm too often underestimates the depth of anaesthesia and does not accurately reflect plasma concentrations. Administering more anaesthetic to try to decrease large BIS values would result in an excessive depth of anaesthesia with delayed awakening and, perhaps, haemodynamic instability. BIS may be well suited to predominantly hypnotic drugs, but it is not useful for the midazolam–fentanyl combination commonly used for cardiac surgery.

References

1 Nordström O, Engström AM, Persson S, Sandin R. Incidence of awareness in total i.v. anaesthesia based on propofol, alfentanil and neuromuscular blockade. *Acta Anaesthiol Scand* 1997; **41**: 978–84

2 Phillips AA, McLean RF, Devitt JH, Harrington EM. Recall of intraoperative events after general anaesthesia and cardiopulmonary bypass. *Can J Anaesth* 1993; **40**: 922–6

3 Polster MR, Gray PA, O'Sullivan G, McCarthy RA, Park GR. Comparison of the sedative and amnestic effects of midazolam and propofol. *Br J Anaesth* 1993; **70**: 612–16

4 Bailey AR, Jones JG. Patients' memories of events during general anaesthesia. *Anesthesia* 1997; **52**: 460–76

5 Bethune DW, Bhosh S, Gray B, Kerr L, Walker IA, Doolan LA, Harwood RJ, Sharples LD. Learning during general anaesthesia: implicit recall after methohexitone or propofol infusion. *Br J Anaesth* 1992; **69**: 197–9

6 Goldman L, Shah MV, Hebden MW. Memory and cardiac anaesthesia. *Anesthesiology* 1987; **42**: 596–603

7 Schwender D, Kaiser A, Klasing S, Peter K, Poppel E. Midlatency auditory evoked potentials and explicit and implicit memory in patients undergoing cardiac surgery. *Anesthesiology* 1994; **80**: 493–501

8 Hilgenberg JC. Intraoperative awareness during high-dose fentanyl–oxygen anesthesia. *Anesthesiology* 1981; **54**: 341–3

9 Jones JG. Hearing and memory in anaesthetised patients. *BMJ* 1986; **292**: 1291–3

10 Dreher H. Mind–body interventions for surgery: evidence and exigency. *Adv Mind–Body Med* 1998; **14**: 207–22

11 Sebel PS. Central nervous system monitoring during open heart surgery: an update. *J Cardiothorac Vasc Anesth* 1998; **12**: 3–8

12 DeDeyne C, Struys M, Decruyenere J, Creuplandt J, Hoste E, Colardyn F. Use of continuous bispectral EEG monitoring to assess depth of sedation in IDU patients. *Intens Care Med* 1998; **24**: 1294–8

13 Thomson AR, Henderson BR, Singh K, Hudson RJ. Concentration–response relationships for fentanyl and sufentanil in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1998; **89**: 852–61

14 Katoh T, Ikeda K. The effects of fentanyl on sevoflurane requirements for loss of consciousness and skin incision. *Anesthesiology* 1998; **88**: 18–24

15 Kazama T, Ikeda K, Morita K. Reduction by fentanyl of the Cp_{50} values of propofol and hemodynamic responses to various noxious stimuli. *Anesthesiology* 1997; **87**: 213–27

16 Van der Maaten JMAA, Epema AH, Gallandat Huet RCG, Hennis PJ. The effect of midazolam at two plasma concentrations on hemodynamics and sufentanil requirement in coronary artery surgery. *J Cardiothor Vasc Anesth* 1996; **10**: 356–63

17 Glass P, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil. *Anaesthesiology* 1997; **86**: 836–47

18 Katoh T, Suzuki A, Ikeda K. Electroencephalographic derivatives as a tool for predicting depth of sedation and anaesthesia induced by sevoflurane. *Anaesthesiology* 1998; **88**: 642–50

19 Doi M, Gajraj RJ, Mantzaridis H, Kenny GN. Effects of cardiopulmonary bypass and hypothermia on electroencephalographic variables. *Anaesthesia* 1997; **52**: 1048–55

20 Barr G, Jakobsson JG, Owall A, Anderson RE. Nitrous oxide does not alter bispectral index: a study with nitrous oxide as sole agent and as adjunct to intravenous anaesthesia. *Br J Anaesth* 1999; **82**: 827–30

21 Iselin-Chaves I, Flaishon R, Sebel P, Howell S, Gan TJ, Sigl J, Ginsberg B, Glass P. The effect of the interaction of propofol and alfentanil on recall, loss of consciousness, and the bispectral index. *Anesth Analg* 1998; **87**: 949–55

22 Mi WD, Sakai T, Singh H, Kudo T, Kudo M, Matsuki A. Hypnotic endpoints vs the bispectral index, 95% spectral edge frequency and median frequency during propofol infusion with or without fentanyl. *Eur J Anaesth* 1999; **16**: 47–52

23 Munte S, Kobbe I, Demertzis A, Lullwitz E, Munte TF, Piepenbrock S, Leuwer M. Increased reading speed for stories presented during general anesthesia. *Anesthesiology* 1999; **90**: 662–9

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Haemodynamic effects of the lateral decubitus position and the kidney rest lateral decubitus position during anaesthesia

M. Yokoyama*, W. Ueda[1] and M. Hirakawa

Department of Anaesthesiology and Resuscitology, Okayama University Medical School, 2-5-1, Shikata-cho, Okayama City, Okayama, 700-8558, Japan
[1]Department of Anaesthesiology and Resuscitology, Kochi Medical School, Kohasu, Okoh-cho, Nankoku City, Kochi, 783, Japan
**Corresponding author*

We measured the haemodynamic effects of changing from the supine position to the lateral decubitus (lateral) position, and then to the kidney rest lateral decubitus (kidney) position in 12 patients undergoing nephrectomy under isoflurane anaesthesia. Eight control patients undergoing pulmonary surgery remained in the lateral position. The lateral position produced no significant changes. In the kidney position, however, significant reductions occurred in the mean arterial ($P<0.01$), right atrial ($P<0.05$) and pulmonary artery wedge pressures ($P<0.01$). There were also significant reductions in cardiac index (from 3.04 (SD 0.21) to 2.44 (0.26) litre min^{-1} m^{-2}, $P<0.01$) and stroke volume index (from 40 (5) to 31 (5) ml beat^{-1} m^{-2}, $P<0.01$). The systemic vascular resistance index increased significantly ($P<0.05$). Cardiac output was probably reduced by a decrease in venous return and an increase in systemic vascular resistance.

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Postural changes during anaesthesia can cause haemodynamic changes with decreases in arterial pressure and cardiac output. For example, the head-up or sitting position can reduce cardiac output.[1–3] However, the effects of the lateral decubitus position (lateral position) on cardiac output in awake non-pregnant patients are not clear.[4–9] Little attention is paid to the effects of the lateral position on cardiac output in healthy subjects other than pregnant women. We know of only one report on the effect of the lateral position in anaesthetized subjects, but measurements were not made in the supine position.[10] The kidney rest lateral decubitus position (kidney position) is commonly used during surgery, and no reports have studied the effects of this position on circulatory variables that might be affected by general anaesthesia.

In the kidney position, patients are placed on their side and arched over a 'kidney rest' in the table with the lower hip flexed. The kidney position, therefore, could cause some blood pooling in the lower extremities. In addition, a 'kidney rest' and flexion of the trunk could compress the large blood vessels. The reduced venous return would decrease the filling pressure and cardiac output.

We examined the haemodynamic effects of changing from the supine position to the lateral position, and then to the kidney position in patients under isoflurane anaesthesia. We also examined the haemodynamic effects in a time-control group, who were kept in the lateral position a longer time to show that the changes in the kidney position were not caused by the passage of time.

Patients and methods

Institutional and ethics committee approvals were obtained, and all participants gave their informed consent. Twenty adult patients (ASA physical status I and II) were included in this study. Twelve of them were scheduled for nephrectomy (kidney group), and the other eight were scheduled for a lung operation (lung group). In the kidney group, six of the 12 underwent right nephrectomy, and the other six underwent left nephrectomy. None of them had cardiovascular diseases or received any medication with haemodynamic effects. The patients were premedicated with hydroxyzine, 50 mg i.m., 1 h before the induction of anaesthesia. Venous and radial arterial cannula were inserted during preoxygenation. Anaesthesia was induced with midazolam, 0.08 mg kg^{-1}, and fentanyl, 2 µg kg^{-1}, i.v., and with inhaled isoflurane and nitrous oxide in oxygen via a semi-closed system. After intratracheal application of 5 ml of 4%

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lidocaine, orotracheal intubation was performed using vecuronium as a muscle relaxant. Anaesthesia was maintained with 0.8% end-tidal isoflurane and 50% nitrous oxide in oxygen. Ventilation was controlled with a tidal volume of 8–10 ml kg^{-1} to maintain the Pa_{CO_2} between 35 and 40 mm Hg.

A thermodilution pulmonary arterial catheter was placed via the right internal jugular vein after the induction of anaesthesia. Chest x-rays were performed to check the position of the catheter. With the patient in the supine position, pressure transducers were referenced to the mid-axillary line at the fourth intercostal space; while the patient was in the lateral position, the transducer was placed level with the junction of the fourth intercostal space and the midsternal line. This is the left atrial level in the lateral position, as described by Kennedy *et al.*[11] Continuous monitoring of PE_{O_2}, PE_{CO_2}, and the end-tidal isoflurane concentration was performed at the tracheal tube with the Datex Capnomac (Datex, Helsinki, Finland). The ECG and the arterial and venous pressures were continuously monitored and recorded.

Measurements were made first with the patient in the supine position. Then all patients were placed in the lateral position on a flat table. In the kidney group, six of the 12 were placed in the right lateral position, and the other six were placed in the left lateral position. A small support was placed just caudal of the dependent axilla to lift the thorax enough to relieve pressure on the axillary neurovascular bundle and to prevent disturbed blood flow to the hand. The dependent leg was flexed at the hip and knee to stabilize the torso, and a head support and leg pillows were added. The second set of measurements was made 5 min after changing the position to lateral.

In the kidney group, patients were then placed in the kidney position (Fig. 1). In this position, the dependent iliac crest is over the hinge between the back and thigh sections of the table, and an elevated rest (kidney rest) is used under this crest. The table top was angulated by 30° to increase the amount of lateral flexion and improve access to the kidney. The third set of measurements was performed 5 min after this change of position. In the lung group, the patients remained in the lateral position, and the third measurements were performed to see if the changes after moving to the kidney position were simply caused by the passage of time. The third measurements in the lung group were taken 10 min after the second measurements because the third measurements in the kidney group were performed about 10 min after the second measurements.

Lactated Ringer's solution was infused at a rate of 20 ml kg^{-1} h^{-1} until the first measurement, and the rate of infusion was kept to a minimum during the measurements. The haemodynamic variables measured in all patients were systolic and diastolic arterial pressures, right atrial pressure (RAP), pulmonary artery systolic and diastolic pressures, pulmonary artery wedge pressure (PAWP), cardiac output (CO) and heart rate (HR). We calculated the mean arterial pressure (MAP), pulmonary artery mean pressure (PAMP), cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI). Cardiac output was measured using the thermodilution technique. Three measurements were made in each position using 10 ml of rapidly injected iced saline and the three measurements were averaged. To avoid the influence of ventilator cycles, measurements were performed at end-expiration.

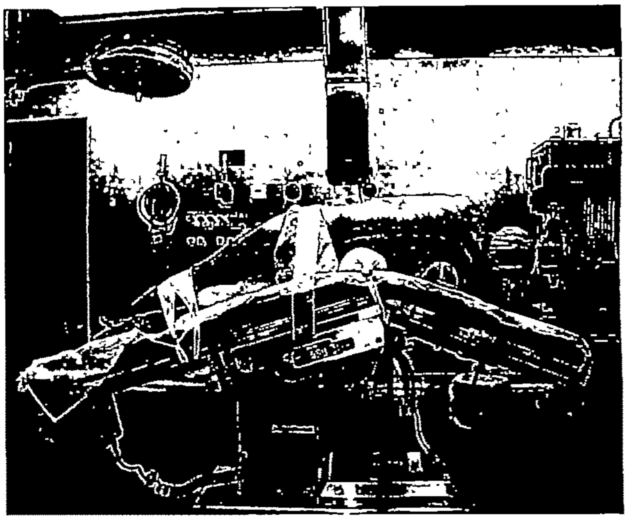

Fig 1 The kidney rest lateral decubitus position. The lower iliac crest is over the hinge between the back and thigh sections of the table, and an elevated rest (kidney rest) is used under this crest The table top was angulated with patients' hips flexed 30° vertically to increase the amount of lateral flexion and improve access to the upper kidney. A small support was placed just caudal of the lower axilla to lift the thorax enough to relieve pressure on the axillary neurovascular bundle and to prevent disturbed blood flow to the hand The lower leg was flexed at the hip and knee to stabilize the torso, and a proper head support and leg pillows were added

Statistical analysis

Data are expressed as mean (SD). Data analysis was performed on a Power Macintosh using Excel 98 and StatView (Version 5). Patients' characteristics were compared using unpaired *t*-test between groups. Haemodynamic measurements in each position were compared using two-way analysis of variance followed by Duncan's method between and within groups. Values were considered statistically significant when $P<0.05$.

Results

Patients' characteristics were similar in the two groups (Table 1). In the kidney group, the postural change from the supine position to the lateral position produced no significant changes in the haemodynamic values (Fig. 2). After the patients were placed in the kidney position, significant reductions in MAP, RAP, PAMP and PAWP were observed, and there was a significant reduction in CI and SVI. HR did not change significantly during the

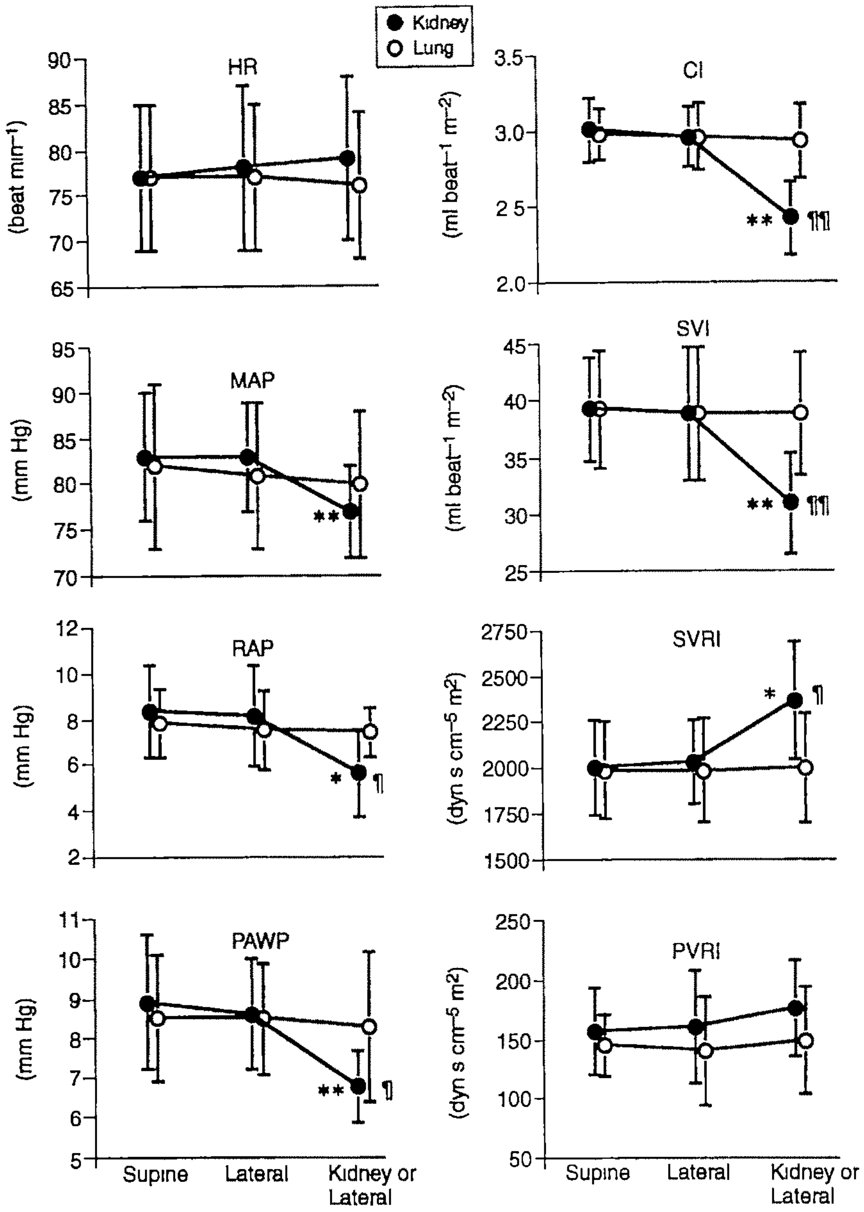

Fig 2 The effect of the postural change on haemodynamic measurements in the kidney and lung groups Measurements were made first with the patient in the supine position (Supine). Then the patients were placed in the lateral decubitus position for the second measurements (Lateral) followed by the kidney rest lateral decubitus position (Kidney) in the kidney group or the lateral decubitus position (Lateral) in the lung group for the third measurements HR, heart rate, MAP, mean arterial pressure; RAP, right atrial pressure; PAWP, pulmonary artery wedge pressure; CI, cardiac index, SVI, stroke volume index; SVRI, systemic vascular resistance index, PVRI, pulmonary vascular resistance index. Values are mean (SD), $n=12$ (the kidney group), $n=8$ (the lung group) *$P<0.05$ *vs* Supine and Lateral, **$P<0.01$ *vs* Supine and Lateral, ¶$P<0.05$ *vs* the lung group, ¶¶$P<0.01$ *vs* the lung group.

Table 1 Patient characteristics Values are mean (SD or range) [95% confidence interval] No significant differences

	Kidney group	Lung group
Number of patients (men, women)	12 (7, 5)	8 (5, 3)
Age (yr)	56 (10) [50–62]	60 (8) [53–67]
Height (cm)	164 (8) [159–169]	162 (8) [155–169]
Weight (kg)	64 (9) [58–70]	64 (9) [56–72]

measurements. After changing to the kidney position, SVRI but not PVRI increased significantly. The haemodynamic variables were similar between the right and left lateral positions and between the right and left kidney positions. In the lung group, the haemodynamic values did not change significantly throughout the measurements (Fig. 2). Between the kidney and the lung groups, there were significant differences in the third measurements with regard to RAP, PAWP, CI, SVI and SVRI.

Discussion

Turning the patients from the lateral to the kidney position caused significant haemodynamic changes. These changes did not occur after changing from the supine to the lateral position, and maintaining the lateral position for extra time did not cause any significant change in the haemodynamic variables. These findings indicate that the kidney position itself has a significant effect on haemodynamic changes.

To determine the effect of the kidney position, Pansard *et al.*[12] measured arterial to end-tidal carbon dioxide tension differences [$Pa\text{-}ET_{CO_2}$] during anaesthesia. They administered anaesthetic agents as required to avoid variations in MAP >10% of stabilized values. The kidney position caused a significant increase in $Pa\text{-}ET_{CO_2}$. They speculated that right filling pressure or CO, or both, which were not monitored, may have decreased because changes in either of these two variables can induce alterations in alveolar dead space.[13 14]

Our results clearly show that CO decreased in the kidney position. Although we could not assess how the kidney position decreased CO, one mechanism would be a reduction in the venous return. The kidney position places the heart at a hydrostatic level above the lower extremities, which can reduce the venous return to the heart. In addition, the 'kidney rest' and flexion of trunk may have compressed the great vessels in the abdomen and disturbed the venous return. The decrease in RAP and PAWP in the kidney position indicated a reduction in the venous return and the resultant decrease in the preload. Although the changes in RAP and PAP were significant, they were quite small, and it is unlikely that the reduction of preload was the only factor contributing to the decrease in CO. Our results showed that the increase in SVRI was also significant and this could certainly contribute to a reduction in CO. It seems likely that the combination of a decrease in the preload and an increase in the afterload resulted in a reduction in the stroke volume and CO, thereby leading to a decrease in MAP. Echocardiography and central aortic pressure monitoring to assess cardiac preload, afterload and cardiac function would be helpful to confirm these possibilities.

In the conscious subject, reflex increases in HR and/or SVR would compensate for the decrease in MAP. In the present study, however, HR did not change significantly during the postural changes indicating that autonomic reflexes were not sufficient. Baroreflex sensitivity is preserved at 0.5 MAC isoflurane but diminished at 1.0 MAC isoflurane,[15] and midazolam[16] and fentanyl also depress the baroreflex.[17] Although we administered only small doses of midazolam and fentanyl about 30 min before the measurements and maintained anaesthesia with 0.8% (0.67 MAC) isoflurane, these drugs might influence the baroreflex.

There are conflicting data about the effects of the supine and lateral positions on CO in non-pregnant human subjects. Investigators have used different techniques to measure CO or have studied patients in different haemodynamic circumstances.[4-9] Atkins *et al.*,[5] using impedance plethysmography, and Newman *et al.*,[7] using a Doppler flowmeter, showed that CO was higher in the supine than in the left or right lateral positions. However, Ueland *et al.*,[4] using dye dilution, found that CO was similar in the supine and lateral positions. Using thermodilution, Whitman *et al.*[6] and Doering and Dracup[8] reported a slightly higher CO in the left lateral than in the supine or right lateral positions, but their findings were based on data obtained from patients immediately after cardiac surgery.

Recently, Lange *et al.*,[9] using thermodilution, observed that CO was similar in the supine and lateral positions in patients whose haemodynamics were stable. Our data, obtained with a thermodilution technique during general anaesthesia, showed that CO was similar in the supine and lateral positions. In haemodynamically stable patients, the lateral position had no clinical effect on haemodynamic variables, even under general anaesthesia. We also found similar measurements in the right and left lateral positions. Recently, Fujise *et al.*[10] reported that MAP, RAP, PAMP and PAWP in the right lateral position were greater than in the left lateral position, but they did not make measurements in the supine position. We speculate that there could have been differences between subjects in the supine position.

In the supine position, we placed the transducer at the level described by Winsor and Birch.[18] In the lateral position, we used the reference level described by Kennedy *et al.*[11] With chest roentgenography, the left atrial level was identified anteriorly at the fourth intercostal space along the midsternal line in the lateral position. Using the lateral left atrial levels, Kennedy *et al.*[11] detected no significant difference between PAP recorded with patients in the lateral position and pressure recorded with patients in the supine position. On the anterior–posterior view of chest roentgenogram in the supine position, the right atrium is at almost the same position as the left atrium, that is, at the fourth intercostal space along the midsternal line. We believe that the fourth intercostal space along the midsternal line will be the reference level of RAP in the lateral position.

In conclusion, our results show that the kidney position during isoflurane anaesthesia causes a significant reduction in CO and MAP.

References

1 Dalrymple DG, MacGowan SW, MacLeod G. Cardiorespiratory effects of the sitting position in neurosurgery. *Br J Anaesth* 1979; **51**: 1079–82

2 Albin MS, Babinski M, Wolf S. Cardiovascular responses to the sitting position. *Br J Anaesth* 1980; **52**: 961–2

3 Coonan TJ, Hope CE. Cardio-respiratory effects of change of body position. *Can Anaesth Soc J* 1983; **30**: 424–38

4 Ueland K, Novy MJ, Peterson EN, Metcalfe J. Maternal cardiovascular dynamics. IV. The influence of gestational age on the maternal cardiovascular response to posture and exercise. *Am J Obstet Gynecol* 1969; **104**: 856–64

5 Atkins AJF, Watt JM, Milan P, Davies P, Crawford JS. The influence of posture upon cardiovascular dynamics throughout pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1981; **12**: 357–63

6 Whitman GR, Howaniak DL, Verga TS. Comparison of cardiac output measurements in 20-degree supine and 20-degree right and left lateral recumbent positions. *Heart Lung* 1982; **11**: 256–7

7 Newman B, Derrington C, Dore C. Cardiac output and the recumbent position in late pregnancy. *Anaesthesia* 1983; **38**. 332–5

8 Doering L, Dracup K. Comparisons of cardiac output in supine and lateral positions. *Nurs Res* 1988; **37**: 114–8

9 Lange RA, Katz J, McBride W, Moore DM, Hillis LD. Effects of supine and lateral positions on cardiac output and intracardiac pressures. *Am J Cardiol* 1988; **62**: 330–3

10 Fujise K, Shingu K, Matsumoto S, *et al.* The effects of the lateral position on cardiopulmonary function during laparoscopic urological surgery. *Anesth Analg* 1998; **87**: 925–30

11 Kennedy GT, Bryant A, Crawford MH. The effects of lateral body positioning on measurements of pulmonary artery and pulmonary artery wedge pressures. *Heart Lung* 1984; **13**: 155–8

12 Pansard JL, Cholley B, Devilliers C, Clergue F, Viars P. Variation in arterial to end-tidal CO_2 tension differences during anesthesia in the 'kidney rest' lateral decubitus position. *Anesth Analg* 1992; **75**: 506–10

13 Gerst PH, Rattenborg C, Holaday DA. The effects of hemorrhage on pulmonary circulation and respiratory gas exchange. *J Clin Invest* 1959; **38**: 524–38

14 Eckenhoff JE, Enderby GEH, Larson A, Edrigde A, Judevin DE. Pulmonary gas exchange during deliberate hypotension. *Br J Anaesth* 1963; **35**: 750–8

15 Muzi M, Ebert TJ. A comparison of baroreflex sensitivity during isoflurane and desflurane anesthesia in humans. *Anesthesiology* 1995; **82**: 919–25

16 Marty J, Gauzit R, Leefevre P, *et al.* Effects of diazepam and midazolam on baroreflex control of heart rate and on sympathetic activity in humans. *Anesth Analg* 1986; **65**: 113–9

17 Kotrly KJ, Ebert TJ, Vucins EJ, *et al.* Effects of fentanyl-diazepam-nitrous oxide anaesthesia on arterial baroreflex control of heart rate in man. *Br J Anaesth* 1986; **58**: 406–14

18 Winsor T, Birch G. Phlebostatic axis and phlebostatic level; reference levels of venous pressure measurements in man. *Proc Soc Exp Biol Med* 1945; **58**: 165–9

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Do fluid administration and reduction in norepinephrine dose improve global and splanchnic haemodynamics?

S. G. Sakka*, A. Meier-Hellmann and K. Reinhart

Department of Anaesthesiology and Intensive Care Medicine, Friedrich Schiller University of Jena,
Bachstrasse 18, D-07740 Jena, Germany

**Corresponding author*

We studied global and splanchnic haemodynamics in patients with septic shock, while reducing norepinephrine doses by progressive fluid loading administration. Ten patients (six female, four male, aged 39–86 yr, mean 61 yr) were assessed using a transpulmonary thermo-dye dilution technique to measure cardiac output, intrathoracic blood volume and total blood volume. Splanchnic blood flow was measured by the steady state indocyanine green technique using a hepatic venous catheter. Gastric mucosal blood flow was estimated by regional carbon dioxide tension ($P\text{R}_{CO_2}$). Hydroxyethylstarch was infused in two stages while maintaining mean arterial pressure, allowing a reduction in norepinephrine dose from 0.54 to 0.33 to 0.21 μg kg^{-1} min^{-1}. Mean (SD) heart rate significantly decreased, from 104 (13) to 94 (15) beats min^{-1}. Total blood volume index (mean (SD)) increased from 2650 (638) to 3655 (885) ml m^{-2}, intrathoracic blood volume index from 888 (204) to 1050 (248) ml m^{-2} and cardiac index from 3.6 (1.0) to 4.0 (0.9) litres min^{-1} m^{-2}. Splanchnic blood flow did not change significantly—either absolute (from 0.81 to 0.98 litres min^{-1} m^{-2}) or fractional (from 22.3% to 23.9%). Gastric mucosal ($P\text{R}_{CO_2}$) increased from 7.5 (2.5) to 9.0 (2.8) kPa. The $P\text{CO}_2$ gap, i.e. the difference between regional and end-tidal $P\text{CO}_2$, increased from 3.1 (2.5) to 4.0 (2.9) kPa. Marked individual variation in responses suggests that norepinephrine dose reduction by fluid loading in patients with stabilized septic shock does not necessarily increase global or splanchnic blood flow.

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Vasopressors are often needed to maintain adequate perfusion pressure in patients with septic shock. Norepinephrine increases urine output in patients with septic shock and hypotension.[1–3] It may improve splanchnic perfusion, when compared with epinephrine or dopamine.[4 5] However, it is widely accepted that volume status should be restored before using vasopressors, and fluid resuscitation of patients with sepsis or septic shock is often guided by the principle of minimizing the need for vasopressor therapy.

In general, sufficient fluids should be given to maximize cardiac output.[6] However, assessment of a patient's volume status and cardiac preload is difficult. Using information obtained by pulmonary artery catheterization to assess cardiac preload may not improve outcome. Other clinical features may be useful to guide fluid therapy. If norepinephrine requirements can be reduced by fluid loading, then a pre-existing fluid deficit may have been present. We therefore investigated whether fluid loading and a decrease in norepinephrine infusion (maintaining mean arterial pressure constant) could improve global and regional blood flow and oxygenation in patients with successfully stabilized septic shock.

Patients and methods

After approval by our institutional review board and informed consent from each patient's next-of-kin, we prospectively studied 10 patients (six female, four male, aged 39–86 yr (mean 61 yr)) who had abdominal sepsis and septic shock according to the criteria of the ACCP-SCCM consensus conference.[7] The mean (SD) simplified acute physiology (SAPS II) score[8] was 48 (9) and sepsis-related organ failure assessment (SOFA) score[9] was 13 (1). Patients were sedated according to body weight with fentanyl 0.4–0.6 mg h^{-1}, dehydroperidol 5.0–7.5 mg h^{-1} and midazolam $\leq$15 mg h^{-1}. In each patient, doses of sedatives remained unchanged during the study period.

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All patients were mechanically ventilated in a pressure-controlled mode (Evita 4; Draeger Werke, Luebeck, Germany) and PEEP (10–15 mbar) was adjusted individually according to blood gas monitoring. Airway pressures remained unchanged throughout the study. In this study, dobutamine doses were kept constant (mean 3.75 $\mu g\ kg^{-1}\ min^{-1}$) and only the norepinephrine was reduced to keep mean arterial pressure constant. No other vasopressors were used.

For haemodynamic monitoring, a femoral artery sheath was inserted in each patient. A 4 French flexible catheter with an integrated thermistor and fibre optic (Pulsiocath 4F, PV 2024L; Pulsion Medical Systems, Munich, Germany) was advanced through the sheath into the abdominal aorta. Intrathoracic blood volume (ITBV) and total blood volume (TBV) were calculated using a computer system (COLD-Z021; Pulsion Medical Systems, Munich, FRG). In this method, ITBV is calculated by the mean transit time approach and TBV by back extrapolation of the aortic indocyanine green (ICG) dilution curve.[10] Each bolus injection used cooled (4–6°C) ICG (Pulsion Medical Systems) 2 mg ml^{-1} (15 ml per bolus). To verify results, each bolus of ICG was followed by two injections of cooled saline. All bolus injections were manual and not related to the ventilatory cycle.

A hepatic venous catheter (7.5 French five-lumen pulmonary artery catheter, Edwards Swan Ganz, CCO/SvO_2, Model 744H 7.5 F; Baxter Healthcare Corporation, Irvine, CA, USA) was inserted from the right internal jugular vein under fluoroscopic control for continuous measurement of oxygen saturation ($ShvO_2$). The correct position of the catheter was verified before and after each study.

Splanchnic blood flow was evaluated by the steady-state ICG (Pulsion Medical Systems) dye technique. Plasma ICG concentrations were assessed spectrophotometrically at a wavelength of 805 nm. Hepatic ICG extraction (E) was calculated from the equation

$$E(\%) = (\text{arterial} - \text{venous ICG concentration})/\text{arterial ICG concentration}$$

and hepatic blood flow (Q_{SPL}) from the equation[11]

$$Q_{SPL} = \text{ICG infusion rate} \times \text{ICG infusate concentration}/(\text{arterial} - \text{venous ICG concentration}) \times (1\text{-haematocrit})$$

Arterial and hepatic venous blood gas samples were immediately analysed for measurement of oxygen and carbon dioxide tensions, pH, haematocrit, haemoglobin concentration, haemoglobin saturation, lactate and glucose levels (Radiometer System 625, Copenhagen, Denmark). Hepatic lactate and glucose exchange were calculated as the product of splanchnic blood flow multiplied by the difference between the liver venous and arterial concentrations.

For the measurement of venous pressures, patients were in the horizontal position and not disconnected from the respirator. As well as continuous measurement of arterial and liver venous blood pressures, we recorded central venous pressure, ITBVI, TBVI, and transpulmonary thermodilution cardiac output. Gastric mucosal ($P\text{R}_{CO_2}$) was measured with a 16 French tonometric probe (Trip NGS catheter; Tonometrics Division, Helsinki, Finland). The patients did not receive enteral nutrition or antacids during the study period. Because of Boerhaave syndrome in patient 6 and erosive gastritis in patient 8, ($P\text{R}_{CO_2}$) was not obtained for those two patients. Systemic oxygen delivery (Do_2I) was calculated from the equation

$$Do_2I = (\text{haemoglobin concentration} \times \text{oxygen saturation} \times 1.36 + \text{oxygen partial pressure} \times 0.0031) \times CI$$

Systemic oxygen consumption (Vo_2I) was measured using a metabolic cart (Deltatrac II; Datex-Engström, Helsinki, Finland). No calorimetric data could be obtained for patient 1 because of technical problems.

Study plan

Following a first ICG bolus of 30 mg, a continuous ICG infusion was started (37.5 mg h^{-1}). After 20, 25 and 30 min of infusion, arterial and hepatic venous blood samples were taken to confirm steady-state conditions of ICG concentrations. After 30 min of ICG infusion, baseline haemodynamic measurements were made. Then fluid was given in two steps by using 200 kDa hydroxyethylstarch 10% (HAES 10 steril; Fresenius AG, Bad Homburg, Germany). Haematocrit was kept constant throughout the study by transfusion of packed red blood cells. The norepinephrine dose was adjusted to keep mean arterial pressure constant. The whole study lasted 4 h, and haemodynamic measurements were obtained at baseline and after 2 and 4 h.

Data analysis

All results are expressed as mean (SD). For between-individual comparison, values were normalized (indexed) by body surface area derived according to DuBois. Statistical analysis was performed using an analysis of variance for repeated measurements and all-pairwise multiple comparison procedure (Student–Newman–Keuls method, SigmaStat). $P<0.05$ was taken as statistically significant.

Results

Global haemodynamic and regional splanchnic oxygenation variables are summarized in Tables 1 and 2. In the first and second steps, respectively, 765 (233) and 705 (222) ml of hydroxyethylstarch were infused. Both fluid administrations caused a significant increase in total blood volume and it was possible to reduce norepinephrine doses without altering mean arterial pressure. To maintain a stable haematocrit, each patient received 2 units of packed red blood cells (each 300 (30) ml) during the 4 h period. Heart rate decreased significantly from 104 (13) to 94 (15) beats

Table 1 Results for global haemodynamic and oxygen transport variables ($n=10$) Pa_{CO_2}, arterial oxygen tension; FI_{O_2}, inspiratory oxygen fraction; Pa_{CO_2}, arterial carbon dioxide tension; HES, hydroxyethylstarch. Norepinephrine doses are presented as mean (median) and 25th–75th percentiles. *Significantly different from baseline value ($P<0.05$), †significantly different from the value at 2 h ($P<0.05$)

	Baseline	**2 h**	**4 h**
Heart rate (beats min^{-1})	104 (13)	99 (15)	94 (15)*†
Arterial pressure (mm Hg)			
Systolic	129 (10)	132 (11)	128 (12)
Diastolic	64 (9)	62 (9)	63 (10)
Mean	84 (9)	84 (8)	83 (9)
Venous pressure (mm Hg)			
Central	11 (5)	15 (7)*	20 (8)*†
Hepatic	13 (6)	18 (7)*	24 (8)*†
Intrathoracic blood volume (ml m^{-2})	888 (204)	1005 (263)*	1050 (248)*
Cardiac index (litres min^{-1} m^{-2})	3.6 (0.8)	4.1 (0.7)	4.0 (0.9)
Stroke volume index (ml m^{-2})	66 (21)	76 (14)*	78 (17)*
Total blood volume index (ml m^{-2})	2650 (638)	3143 (734)*	3655 (885)*†
Systemic vascular resistance (dyn s cm^{-5} m^{-2})	1650 (328)	1381 (227)*	1310 (247)*
Extravascular lung water (ml kg^{-1})	8.4 (4.0)	7.9 (4.0)	8.5 (3.8)
Pa_{O_2} (kPa)	12.81 (3.85)	13.90 (4.11)	12.84 (4.82)
FI_{O_2} (%)	34 (3)	35 (4)	36 (5)
Pa_{CO_2} (kPa)	5.21 (0.47)	5.57 (0.60)*	6.03 (0.57)*†
Systemic oxygen delivery (ml min^{-1} m^{-2})	525 (108)	553 (126)	540 (154)
Systemic oxygen consumption (ml min^{-1} m^{-2})	139 (28)	144 (27)	140 (26)
Haematocrit (%)	33 (5)	31 (3)	33 (3)
Norepinephrine (μg kg^{-1} min^{-1})	0.54 (0.25)	0.33* (0.12)	0.21* (0.06)
	0.18–1.01	0.10–0.66	0.06–0.43
HES infusion volume (ml)		765 (233)	705 (222)

Table 2 Splanchnic haemodynamic and oxygen transport variables ($n=10$) ICG, indocyanine green. PET_{CO_2}, end tidal carbon dioxide tension Values for fractional splanchnic blood flow are presented as mean (median) and 25th–75th percentiles. Hepatic lactate and glucose exchange were calculated by multiplication of the hepatic venous–arterial concentration difference and splanchnic blood flow. *Significantly different from baseline value ($P<0.05$), †significantly different from value at 2 h ($P<0.05$)

	Baseline	**2 h**	**4 h**
Splanchnic blood flow (litre min^{-1} m^{-2})	0.81 (0.6)	1.02 (0.9)	0.98 (0.7)
Fractional splanchnic blood flow (%)	22.3 (21.8)	23.8 (19.7)	23.9 (21.7)
	11.5–28.2	10.3–31.4	7.7–37.4
Splanchnic oxygen delivery (ml min^{-1} m^{-2})	125 (97)	145 (143)	136 (109)
Splanchnic oxygen consumption (ml min^{-1} m^{-2})	62 (32)	61 (40)	57 (35)
Splanchnic oxygen extraction ratio (%)	56.1 (18.0)	52.7 (17.8)	52.6 (21.1)
Lactate exchange (mmol min^{-1} m^{-2})	−0.35 (0.4)	−0.30 (0.5)	−0.30 (0.6)
Glucose exchange (mmol min^{-1} m^{-2})	0.14 (0.4)	−0.02 (0.7)	0.16 (0.3)
PR_{CO_2} (kPa)	7.5 (2.5)	8.2 (2.9)*	9.0 (2.8)*†
PET_{CO_2} (kPa)	4.5 (0.7)	4.9 (0.7)*	5.1 (0.7)*
P_{CO_2}-gap (kPa)	3.1 (2.5)	3.3 (2.9)	4.0 (2.9)*†

min^{-1}, while central venous and hepatic venous pressure increased significantly after each fluid administration. ITBVI increased from 888 (204) to 1050 (248) ml m^{-2}. Stroke volume index increased significantly, from 66 (21) to 76 (14) and finally to 78 (17) ml m^{-2}, while cardiac index increased from 3.6 (1.0) to 4.0 (0.9) litre min^{-1} m^{-2} during the study period. TBVI increased from 2650 (638) to 3655 (885) ml m^{-2}. Although mean splanchnic blood tended to be higher after fluid loading, neither absolute splanchnic blood flow (which changed from 0.81 to 0.98 litre min^{-1} m^{-2}) nor fractional splanchnic blood flow (from 22.3% to 23.9%) changed significantly at either stage. The individual data showed that, in some patients, cardiac index and absolute splanchnic blood flow even decreased (Fig. 1). The difference between regional and end-tidal P_{CO_2} (P_{CO_2} gap) increased from 3.1 (2.5) to 3.3 (2.9) and 4.0 (2.9) kPa.

For each measuring point, variation coefficients were 6.0 (2.9) %, 4.2 (2.6) % and 4.3 (3.7) % for arterial ICG concentrations and 5.0 (3.0) %, 4.8 (2.6) % and 6.6 (4.6) % for hepatic venous ICG concentrations.

Discussion

These data show that, in patients with haemodynamically stabilized septic shock, reduction in norepinephrine infusion after fluid loading did not increase splanchnic blood flow. Intrathoracic blood volume increased; this is a more appropriate measure than the cardiac filling pressures to assess cardiac preload in the critically ill.[12–14] We conclude that the fluid increased cardiac preload in our patients. As the norepinephrine dose could be reduced in every patient while mean arterial pressure remained constant, pre-existing fluid deficit was likely. Nevertheless, marked individual differ-

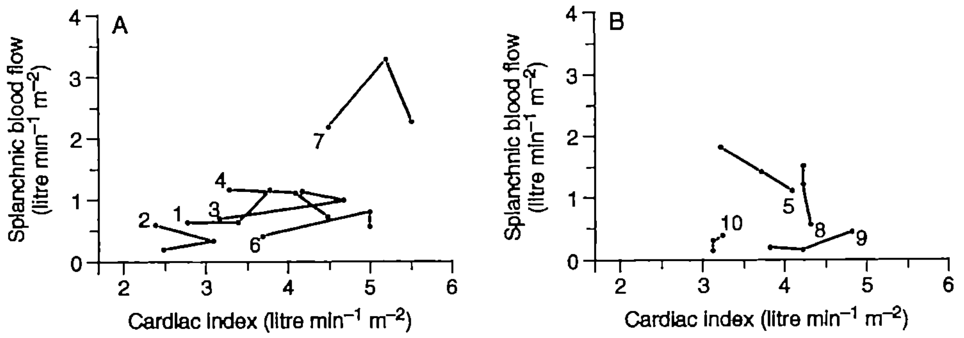

Fig 1 Cardiac index and absolute splanchnic blood flow in 10 patients undergoing fluid loading associated with a norepinephrine dose reduction and stable mean arterial pressure. (A) Patients in whom cardiac output increased; (B) those in whom cardiac output decreased. The patient's number indicates the beginning of an individual course.

ences in global and splanchnic haemodynamics were found after fluid was given. Fluid administration and vasopressor dose reduction did not always increase cardiac index. Some patients had increased splanchnic perfusion with increased cardiac index, but other patients did not. Thus, fluid loading and a reduction in vasopressor support with a constant mean arterial pressure are not always associated with improved global or regional perfusion. Furthermore, regional carbon dioxide tension and carbon dioxide gap increased significantly during fluid loading, which may suggest a reduction in splanchnic blood flow or could be interpreted as a consecutive 'washout phenomenon'.

Norepinephrine increases splanchnic vascular resistance and thus decreases splanchnic blood flow in animals and humans in non-septic conditions.[15 16] Bersten and colleagues[16] did not find a redistribution of blood flow with norepinephrine infusion, away from the kidneys, liver and pancreas, in septic animals. Norepinephrine can improve splanchnic oxygenation by increasing mean arterial pressure in septic patients.[4] Patients receiving norepinephrine had an increase in gastric mucosal pH (pH_i), indicating an increase in microcirculatory perfusion, whereas dopamine caused a decrease in pH_i. Thus, norepinephrine seems to have some potential positive effects on splanchnic blood flow in patients with sepsis. However, mean arterial pressure was constant in this study, so perfusion pressure alone does not appear to cause these benefits.

Nevertheless, these results should not be interpreted as showing that fluid resuscitation, which is still one of the most important supportive treatments in sepsis, is less beneficial than norepinephrine therapy. In our patients, mean splanchnic blood flow tended to be greater after fluid loading. According to recent recommendations, optimization of cardiac output is a major goal in treatment of patients with sepsis and vasopressors should only be used after sufficient fluid resuscitation.[17] In this study, we did not determine individual Frank–Starling curves in order to optimize cardiac output. Instead, we focused on reduced norepinephrine doses by fluid loading. Since cardiac index decreased in some patients during fluid loading with a reduction in norepinephrine, we cannot exclude fluid overload in some of our patients. Fluid overload may have contributed, since total blood volume increased from normal to supranormal values during the study period. Furthermore, central venous and hepatic venous pressures increased to very high levels, which may impair splanchnic blood flow by the reduced perfusion pressure gradient. Animal studies[18] showed that sinusoidal pressure in the liver increases considerably with increasing central venous pressure and that the portion of the central venous pressure transmitted to the sinusoids increases exponentially. Thus, impaired hepatic venous drainage may have reduced gastric and splanchnic blood flow in some patients. Finally, individual differences in central venous pressure and splanchnic perfusion pressure may explain the individual variations in splanchnic blood flow. A major limitation of our study is the lack of a control group, which would have allowed comparison of these data on splanchnic blood flow with septic shock patients who remained fluid depleted.

Septic patients respond in different ways to vasoactive substances.[19 20] In these studies, the effects of norepinephrine and low-dose dopamine on splanchnic blood flow were unpredictable between different individuals. Our results support these observations: septic patients do not respond uniformly to therapeutic interventions.

Conclusion

A decrease in norepinephrine dose following fluid administration cannot be interpreted as a sign of improved global or regional blood flow. Further studies are needed to understand the differing response of splanchnic perfusion among patients, and to identify the most appropriate dose of vasopressor for the individual patient.

References

1 Desjars P, Pinaud M, Potel G, Tasseau F, Touze MD. A reappraisal of norepinephrine therapy in human septic shock. *Crit Care Med* 1987; **15:** 134–7

2 Hesselvik JF, Brodin B. Low dose norepinephrine in patients with septic shock and oliguria: effects on afterload, urine flow, and oxygen transport. *Crit Care Med* 1989; **17:** 179–80

3 Martin C, Eon B, Saux P, Aknin P, Gouin F. Renal effects of

norepinephrine used to treat septic shock patients. *Crit Care Med* 1990; **18:** 282–5

4 Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *JAMA* 1994; **272:** 1354–7

5 Meier-Hellmann A, Reinhart K, Bredle DL, Specht M, Spies CD, Hannemann L. Epinephrine impairs splanchnic perfusion in septic shock. *Crit Care Med* 1997; **25:** 399–404

6 Shoemaker WC, Appel P, Bland R. Use of physiologic monitoring to predict outcome and to assist in clinical decisions in critically ill postoperative patients. *Am J Surg* 1983; **146:** 43–8

7 American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; **20:** 864–74

8 Le Gall JR, Lemeshow S, Saulnier F A new simplified acute physiology score (SAPS II) based on a European/ North American multicenter study. *JAMA* 1993; **270:** 2957–63

9 Vincent J-L, Moreno R, Takala J. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/ failure. *Intensive Care Med* 1996; **22:** 707–10

10 Hoeft A. Transpulmonary indicator dilution: an alternative approach for hemodynamic monitoring. In: Vincent J-L, ed. *Yearbook of Intensive Care and Emergency Medicine 1995*. Berlin-Heidelberg-New York: Springer-Verlag, 1995; 593–605

11 Uusaro A, Ruokonen E, Takala J. Estimation of splanchnic blood flow by the Fick principle in man and problems in the use of indocyanine green. *Cardiovasc Res* 1995; **30:** 106–12

12 Hoeft A, Schorn B, Weyland A, Scholz M, Buhre W, Stepanek E, Allen SJ, Sonntag H. Bedside assessment of intravascular volume status in patients undergoing coronary bypass surgery. *Anesthesiology* 1994; **81:** 76–86

13 Lichtwarck-Aschoff M, Zeravik J, Pfeiffer UJ. Intrathoracic blood volume accurately reflects circulatory volume status in critically ill patients with mechanical ventilation. *Intensive Care Med* 1992; **18:** 142–7

14 Sakka SG, Bredle DL, Reinhart K, Meier-Hellmann A. Comparison between intrathoracic blood volume and cardiac filling pressures in the early phase of hemodynamic instability of patients with sepsis or septic shock. *J Crit Care* 1999, **14:** 78–83

15 Granger DN, Richardson PDI, Kvietys PR, Mortillaro NA. Intestinal blood flow. *Gastroenterology* 1980; **78:** 837–63

16 Bersten AD, Hersch M, Cheung H, Rutledge FS, Sibbald WJ. The effect of various sympathomimetics on the regional circulations in hyperdynamic sepsis. *Surgery* 1992; **112:** 549–61

17 Task Force of the American College of Critical Care Medicine/ Society of Critical Care Medicine. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. *Crit Care Med* 1999; **27:** 639–60

18 Lautt WW, Greenway CV, Legare DJ. Effect of hepatic nerves, norepinephrine, angiotensin, and elevated central venous pressure on postsinusoidal resistance sites and intrahepatic pressures in cats. *Microvasc Res* 1987; **33:** 50–61

19 Ruokonen E, Takala J, Kari A, Saxen H, Mertsola J, Jansen EJ. Regional blood flow and oxygen transport in septic shock. *Crit Care Med* 1993; **21:** 1296–303

20 Meier-Hellmann A, Bredle DL, Specht M, Spies C, Hannemann L, Reinhart K. The effects of low-dose dopamine on splanchnic blood flow and oxygen uptake in patients with septic shock. *Intensive Care Med* 1997; **23:** 31–7

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Serum myoglobin and creatine kinase following surgery

A. S. Laurence

Royal Preston Hospital, Preston PR2 4HT, UK

Serum myoglobin (by radioimmunoassay) and creatine kinase were measured for up to 7 days in 30 patients following surgical procedures, including total hip replacement and bilateral subcostal abdominal incisions. Serum myoglobin reached a maximum of 1390 μg litre^{-1} (median 345 μg litre^{-1} for major surgery patients) on the first postoperative day but levels were still elevated by day 7 in some patients. Creatine kinase reached a maximum of 1339 i.u. litre^{-1} at day 2 (median 422 i.u. litre^{-1} for major surgery patients), generally peaking 1 day after myoglobin in individual patients. These values may have significance when investigating a suspicion of coincident perioperative events such as myocardial infarction or malignant hyperthermia.

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Blood concentrations of intracellular proteins, in particular myoglobin and creatine kinase (CK), are increased after muscle is damaged by physical or biochemical injury. This has been reported following crush injury,[1] myocardial infarction,[2–5] malignant hyperthermia (MH),[6 7] or other rare reactions.[8] Modest increases follow the routine administration of succinylcholine.[9–12] Serum concentrations of CK and possibly myoglobin may be useful in support of a provisional diagnosis of an acute episode of MH.[13] However, any other concurrent event that might also cause damage to muscle could confuse the biochemical picture. In particular, surgery might have started, or preoperative trauma might be the cause of raised CK and myoglobin. The serum CK and myoglobin concentrations and the changes with time following myocardial infarction and succinylcholine administration are well documented, but those due to surgery are not.

Methods

Patients ASA I–III presenting for various elective or scheduled surgical procedures gave verbal consent for several extra blood samples to be taken before, during and after surgery in addition to those routine specimens associated with their management. All patients were expected to be in hospital for up to a week or more after the operation. Following routine premedication with oral lorazepam, patients arrived in the anaesthetic room and a cannula was placed in a suitable vein for a preinduction blood sample and induction of anaesthesia. Anaesthesia was induced using thiopentone and an opioid. A non-depolarizing neuromuscular blocking drug was used to facilitate tracheal intubation and the lungs were mechanically ventilated with nitrous oxide, oxygen and an inhalation anaesthetic supplement. Surgical diathermy was used as required by the surgeon. At the conclusion of surgery, a second blood sample was drawn, either from the original cannula or from a separate site as required. Postoperative analgesia was provided by i.m. opioid and anti-emetics as required. Postoperative fluids and blood administration were managed as dictated by clinical requirements.

On the subsequent postoperative days several blood samples were obtained from the patients as part of their routine postoperative care. The remaining serum from these samples was collected from the biochemistry or haematology laboratory. On other postoperative days an additional sample was taken for the purposes of the study. All patients thereby had daily blood samples up to day 4 Thereafter, most patients in the major surgery group had blood taken up to the seventh postoperative day.

All samples were separated and frozen prior to assay in batches for myoglobin and CK. Myoglobin was assayed by radioimmunoassay using duplicate determination of samples. Coefficient of variation was typically 11%. Values above 300 μg litre^{-1} required dilution and reassay to bring them within the range of the assay (10–250 μg litre^{-1}). CK was assayed by a standard NADP/NADPH colorimetric measurement of reaction rate at 37 °C (Boehringer Mannheim).

Results

A total of 30 patients was studied. They were divided into two groups; minor muscle-cutting surgery and major muscle-cutting surgery, based on the subjective impression

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This work was carried out at the Northern General Hospital, Sheffield.

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of the degree of muscle involvement of the surgical procedure. The number of patients and procedures in each group is shown in Table 1. No patient gave any clinical suspicion of peri- or postoperative myocardial infarction.

Mean serum myoglobin and CK concentrations over the perioperative period are summarized in Table 2. Preinduction values for all patients were close to the normal ranges for myoglobin (6–85 µg litre^{-1}) and CK (10–180 i.u. litre^{-1}), respectively. The individual values for myoglobin and CK are plotted graphically in Figure 1 for the minor surgery group and Figure 2 for the major surgery group. The maximum myoglobin concentration was 1390 µg litre^{-1} on day 1 in a patient having a thoraco-abdominal resection. The maximum CK concentration was 1339 i.u. litre^{-1} on day 2 in a patient having a latissimus dorsi flap transfer. In most subjects, the CK reached its maximum value 1 day after that for myoglobin.

Discussion

We have demonstrated that marked changes in serum myoglobin and CK can occur following muscle-cutting surgery. These values can be considerably greater than those found following a single administration of succinylcholine in adults[9 12] or children,[10] comparable to that following an MI but considerably less than that following a typical episode of MH.[6 7]

No attempt was made to rigidly control the type of surgery. It was considered important that representative biochemical values following a range of surgical procedures were identified. We avoided the potentially confounding effect of succinylcholine. The distinction between minor and major muscle-cutting procedures was based on the apparent extent of muscle involved. It can be seen that some subjects in the minor group had substantial changes, while a few in the major group had minimal changes. Presumably a surgical incision apparently avoiding muscle (e.g. an abdominal midline incision through the linea alba) can still result in muscle being caught in sutures used for closure.

Table 1 Surgical procedures

	Operation	Number
Minor muscle	Simple mastectomy	4
Cutting	Midline abdominal incision	9
Surgery	Knee replacement	1
Major muscle	Thoraco abdominal resection	3
Cutting	Bilateral subcostal incision	5
Surgery	Latissimus dorsi flap	2
	Total hip replacement	4
	Laminectomy	1

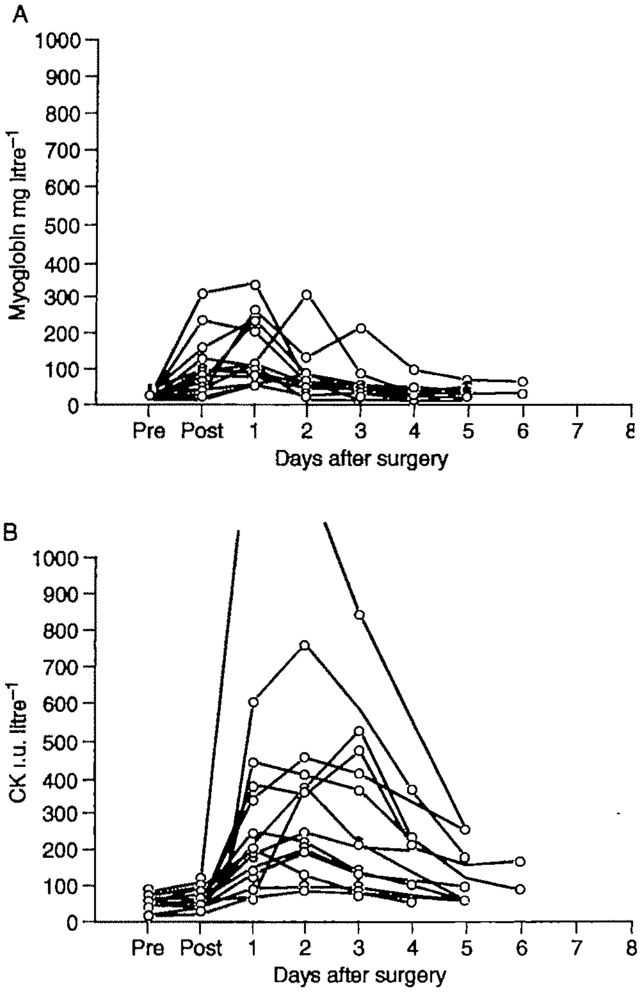

Fig 1 Serum myoglobin (A) and creatine kinase, CK (B) concentrations for individual patients in the minor surgery group. The 'Pre' sample was taken immediately prior to induction of anaesthesia and the 'Post' sample at the completion of surgery.

Table 2 Median (range) myoglobin (µg litre^{-1}) and CK (i.u. litre^{-1}) values

	Minor surgery		Major surgery	
	Myoglobin	CK	Myoglobin	CK
Pre-ind	20 (6–42)	40 (9–76)	33 (3–100)	42 (9–114)
Postop	77 (12–310)	47 (11–99)	315 (52–853)	114 (37–440)
Day 1	108 (50–342)	195 (57–1296)	345 (132–1390)	609 (133–968)
Day 2	60 (10–310)	283 (73–1289)	178 (66–327)	422 (156–1339)
Day 3	39 (10–219)	196 (60–833)	82 (36–302)	256 (38–1208)
Day 4	25 (9–97)	181 (32–208)	51 (18–118)	150 (49–1044)
Day 5	30 (7–67)	84 (31–230)	39 (17–132)	83 (16–329)
Day 6			44 (21–108)	84 (9–260)
Day 7			36 (15–99)	54 (22–163)

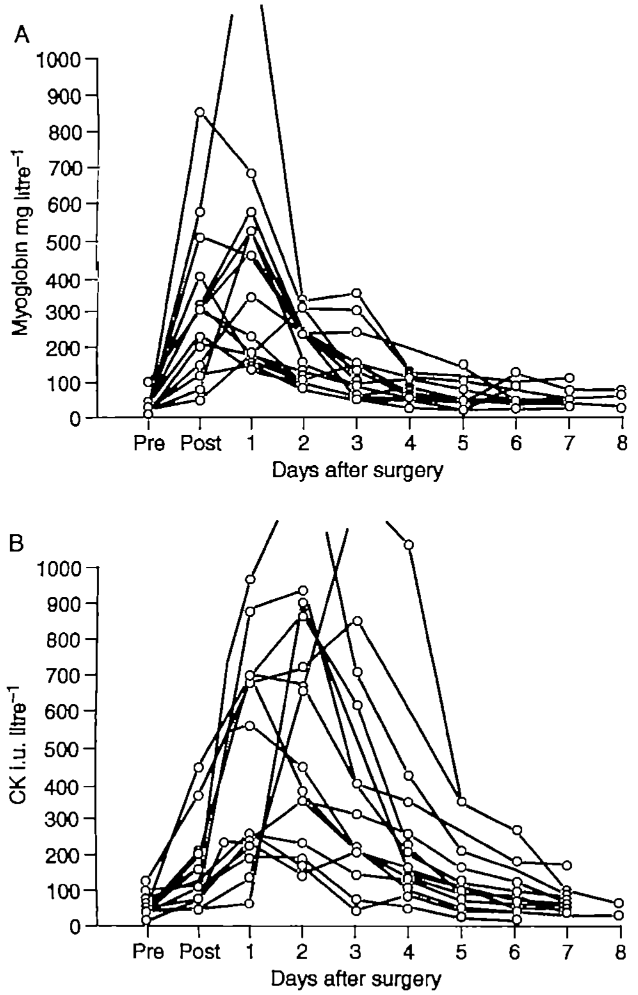

Fig 2 Serum myoglobin (A) and CK (B) concentrations for individual patients in the major surgery group The 'Pre' sample was taken immediately prior to induction of anaesthesia and the 'Post' sample at the completion of surgery

It is possible that other circumstances after surgery, such as tissue infection, hypoperfusion and severe biochemical abnormalities could affect the concentration of muscle proteins in the circulation. None of these events is thought to have been present in our patients. There are also a number of other factors which could have affected our results. CK and possibly myoglobin denature at room temperature, and some samples had been in the biochemistry laboratory for 24 h before being frozen. Some preoperative values may have been elevated slightly by the pathology for which the patient was having surgery, while some postoperative values may have been influenced by the state of postoperative hydration. None of these factors would have affected the myoglobin and CK concentrations by a large factor, however, compared to the magnitude of postoperative changes due to surgery.

The highest myoglobin levels we found (1300 μg litre^{-1}) following surgery are unlikely to cause any clinical derangement. Levels of at least 50 000 μg litre^{-1} are probably necessary to cause acute renal failure,[14] although if the patient is treated promptly with no other confounding factors, levels of 47 000 μg litre^{-1} have been found to cause no renal impairment.[6]

The serum concentrations of myoglobin and CK we have found following surgery are not clinically significant, but could cause diagnostic confusion in a patient with myocardial infarction or MH. Following major trauma or extensive surgery, postoperative concentrations could be much greater than found in our study. Modest trauma induced in live pigs by firing high-velocity metal fragments into muscle results in a rise of CK to over 4000 i.u. litre^{-1} within 6 h, falling towards normal values at 3 days.[15]

A case of suspected perioperative myocardial infarction can usually be confirmed by CK isoenzyme tests, but isoenzyme results usually take several days to obtain. The biochemical evidence to support a suspected MH episode could be confused by raised levels caused by major surgery, severe trauma or myocardial infarction. CK estimation is easier to undertake than radioimmunoassay of serum myoglobin, and is frequently measured following anaesthetic reactions. It is worth noting that the maximum myoglobin values in μg litre^{-1} are usually numerically similar to the later maximum CK values in i.u. litre^{-1} for a range of muscle insults, including this present study. Therefore CK estimation, taking into account the time course of its release, can be used as an alternative to myoglobin estimations following suspected anaesthetic reactions.

In conclusion, we suggest that serum CK estimation, as long as the peak value has been obtained, can be a valid indication of the extent of muscle damage. Interpretation of postoperative (e.g. 24 h) CK values should therefore take into account the possible influence of trauma or muscle-cutting surgery.

References

1 Bywaters EGL Ischaemic muscle necrosis ('crush syndrome'). *Br Med Bull* 1945; **3**: 107–10
2 Stone MJ, Willerson JT, Gomez-Sanchez CE, Waterman MR Radio Immunoassay of myoglobin in human serum. Results in patients with acute myocardial infarction. *J Clin Invest* 1975; **5**: 1334–9
3 Drexel H, Dworzak E, Kirchmair W, Milz MM, Puschendorf B, Dienstl F. Myoglobinemia in the early phase of acute myocardial infarction. *Am Heart J* 1983; **105**: 642–51
4 Keffer JH. Myocardial markers of injury. Evolutions and insights. *Am J Clin Chem* 1995; **105**; 303–20
5 Tormey WP. The diagnosis and management of acute myocardial infarction – a role for biochemical markers. *Ann Clin Chem* 1996: **33**: 477–81
6 Laurence AS, Vanner GK, Collins W, Hopkins PM. Serum and urinary myoglobin following an aborted malignant hyperthermia reaction *Anaesthesia* 1996; **51**: 958–61
7 Ramirez-R JA, Cheetham ED, Laurence AS, Hopkins P. Suxamethonium, masseter spasm and later malignant hyperthermia. *Anaesthesia* 1998; **53**: 1111–6
8 Wight JP, Laurence AS, Holt S, Forrest ARW Rhabdomyolysis with hyperkalaemia after aminophylline overdose. *Med Sci Law* 1987; **27**: 103–5

9 Laurence AS. Biochemical changes following suxamethonium. Serum myoglobin potassium and creatine kinase changes before commencement of surgery. *Anaesthesia* 1985; **40**: 854–9

10 Laurence AS. Serum myoglobin release following suxamethonium administration to children. *Eur J Anaesthesia* 1988; **5**: 31–8

11 Laurence AS. Myalgia and biochemical changes following intermittent suxamethonium administration; effect of alcuronium, lignocaine, midazolam and suxamethonium pretreatments on myoglobin, creatine kinase and myalgia. *Anaesthesia* 1987; **42**: 503–10

12 Laurence AS, Norris S. Orthopaedic tourniquets and anaesthesia. Serum myoglobin as an indication of tourniquet muscle damage. *Eur J Anaesthesiology* 1998; **5**: 31–8

13 Ellis FR, Halsall PJ, Harriman DGF. The work of the Leeds Malignant Hyperpyrexia unit, 1971–84. *Anaesthesia* 1986; **41**: 809–15

14 Wakabayashi Y, Kikuno T, Ohwada T, Kikawada R. Rapid fall in blood myoglobin in massive rhabdomyolysis and acute renal failure. *Intensive Care Med* 1994; **20**: 109–12

15 Bowyer GW. Management of small fragmentation wounds in modern warfare: a return to Hunterian principles? *Ann Royal Col Surgeons Engl* 1997; **79**: 175–82

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Ignorance of post-exposure prophylaxis guidelines following HIV needlestick injury may increase the risk of seroconversion

P. Diprose*, C. D. Deakin and J. Smedley

Department of Anaesthetics, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK

**Corresponding author*

Needlestick injury is relatively common amongst healthcare workers, particularly those, such as anaesthetists, who regularly perform invasive procedures. The risk of seroconversion following needlestick injury may be reduced by knowledge of body fluids that are high risk and knowledge of post-exposure prophylaxis following possible HIV-contaminated needlestick injury. A structured questionnaire was used to establish knowledge regarding high HIV risk body fluids and measures to be taken following needlestick injury in anaesthetists working in a large teaching hospital. Completed questionnaires were obtained from all 76 anaesthetists working in the department (39 consultant, 37 trainee/non-consultant). Only 45.2% correctly identified high-risk body fluids. Sixty-eight per cent of anaesthetists knew the appropriate first aid measures to be taken following needlestick injury. Only 15% of anaesthetists were aware that post-exposure prophylaxis (oral medication) should be administered within 1 h of injury. This study reveals a surprisingly poor knowledge of high-risk body fluids and action to be taken following needlestick injury. Timely post-exposure prophylaxis, after needlestick exposure to high-risk body fluids, is believed to reduce the risk of seroconversion to HIV. Ignorance of this may increase the risk of seroconversion to HIV for anaesthetists and other healthcare professionals.

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Needlestick injury from patients with known or suspected HIV infection is an important occupational risk for healthcare workers. The incidence of all injuries varies between occupational groups but is particularly prevalent in those regularly performing invasive procedures. Factors that determine risk of significant exposure to HIV include the frequency of needlestick incidents and the prevalence of HIV infection in the patient population.[1] Risk of transmission of HIV from a single exposure to infected material depends on the size and the type of inoculum. Known inoculation risk factors include deep injury, hollow bore needles, blood from terminally ill HIV patients, and needles that have been in arteries or veins. Overall, the risk of acquiring HIV following needlestick injury from HIV infected blood has been estimated at three per 1000 injuries.[2 3] The estimated yearly risk of HIV infection for anaesthetists in the US, for example, has been put at between 0.00013 and 0.032% depending on the seroprevalence of HIV infection within the patient population.[4]

In 1997 the Department of Health issued guidelines for health care workers on the management of occupational exposure to HIV.[5] The guidelines recommended that post-exposure prophylaxis, in the form of triple therapy usually with zidovudine, lamivudine and indinavir, be offered to health care workers following high-risk needlestick injury with the aim of minimizing the risks of developing HIV infection. The guidelines emphasize that if post-exposure prophylaxis is to be most effective it should be commenced as soon as possible after the exposure and ideally within 1 h of injury.

Despite clear guidelines, health care workers generally take inadequate measures following needlestick injury. For example, in a survey in the US only 45.4% of anaesthetists who sustained a needlestick injury that had some form of blood or high-risk fluid contamination sought any form of treatment.[6] This audit aimed to discover whether anaesthetists within a large teaching hospital in the UK appreciated the risks from, and understood the necessary action following, needlestick injury particularly following the 1997 post-exposure prophylaxis guidelines.

The host Trust has a multi-disciplinary occupational health and safety service that is led by a consultant occupational physician. A comprehensive mechanism for timely management of occupational exposure to blood and body fluids has been in place since December 1996. Arrangements include a written policy on the management of needlestick

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and contamination incidents, a priority telephone 'hotline' for urgent reporting of incidents, 24 h access to urgent risk assessment and treatment of exposures (including advice from medical experts), and long-term counselling and follow-up by occupational health professionals. These systems were designed to ensure access to post-exposure prophylaxis for high-risk HIV exposures within 1 h of the incident. The policy was supported by an education programme comprising a letter to all trust employees, verbal presentation at induction for all junior doctors, verbal presentation and a written handout for consultant medical staff, and periodic poster and publicity campaigns. A verbal presentation covering the issue of occupational transmission of blood-borne infection and the local arrangements for management of contamination incidents was given at an anaesthetic department seminar in 1998. Approximately 6 months later this questionnaire survey was undertaken to determine knowledge of which body fluids are high risk for HIV transmission, appropriate first aid treatment immediately following exposure, and how soon after injury post-exposure prophylaxis should be commenced.

Materials and methods

Following ethics committee approval, a questionnaire was sent to all grades of anaesthetist (76 subjects) working for Southampton University Hospitals NHS Trust. This questionnaire asked the following.

1. What percentage of needlestick injuries from patients with known HIV infection are likely to result in transmission of the virus to the recipient?
2. Which of the following nine body fluids (presuming that they are not blood stained) may be considered as 'high risk' for the transmission of HIV: breast milk, synovial fluid, saliva, faeces, urine, peritoneal fluid, pleural fluid, vomit, cerebrospinal fluid?
3. Who should be contacted in the event of a needlestick injury?
4. What two first aid procedures should you perform to the needlestick site?
5. How soon after a 'high risk' needlestick injury should post-exposure prophylaxis commence?

Any non-responders from the initial survey were sent a further questionnaire and then if necessary were directly approached. Differences between consultant and trainee/non-consultant grades were analysed using a chi-squared test.

Results

Completed questionnaires were obtained from 37 juniors (100%) and 39 consultants (98%).

1. What percentage of needlestick injuries from patients with known HIV infection are likely to result in transmission of the virus to the recipient?

The risk of a needlestick injury from a patient with HIV resulting in seroconversion is estimated to be around three per 1000 injuries. Overall, only 26 (34%) anaesthetists were aware of the true risk (between 1:1000 and 9:1000 injuries) of transmission of HIV from a needlestick injury. Of all respondents, 17 (22%) overestimated the risk compared with 33 (43%) who underestimated the risk.

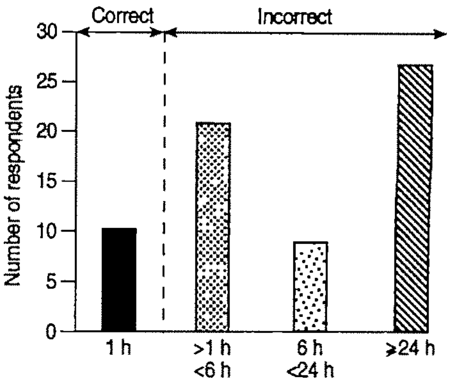

Fig 1 Recommended time to first dose of post-exposure prophylaxis.

2. Which of the following nine body fluids (presuming that they are not blood stained) may be considered as 'high risk' for the transmission of HIV: breast milk, synovial fluid, saliva, faeces, urine, peritoneal fluid, pleural fluid, vomit, cerebrospinal fluid?

For the high risk fluids (CSF, pleural, peritoneal, synovial, breast milk) only 14 (35%) consultant anaesthetists and 18 (49%) juniors correctly identified them as high risk. For low risk fluids (vomit, urine, faeces, saliva), 16 (41%) consultants and 21 (57%) juniors correctly identified the low risk fluids. Trainees/non-consultant grades were better than consultants in their knowledge of both high risk fluids ($P<0.02$) and low risk fluids ($P<0.01$).

3. Who should be contacted in the event of a needlestick injury?

Thirty-eight out of 39 consultants (97%) and all trainees/non-consultant grades correctly stated either the Accident and Emergency Department or the Occupational Health Department.

4. What two first aid procedures should you perform to the needlestick site?

Following a needlestick injury the first priority should be to promote active bleeding of the wound and to wash the wound thoroughly with soap and running water. Overall, 68% of anaesthetists (25/39 consultants; 26/37 trainees/non-consultant grades) correctly stated both measures.

5. How soon after a 'high risk' needlestick injury should post-exposure prophylaxis commence?

Only 10 out of 76 anaesthetists (15%) were aware that post-exposure prophylaxis following an HIV prone needlestick infection should be started within 1 h of the injury. Results are shown in Figure 1. Forty per cent (37/67) of anaesthetists who answered the question believed that post-exposure prophylaxis could be delayed for 24 h or more.

Discussion

The general understanding of HIV transmission in terms of high-risk body fluids, risks from needlestick injury, and appropriate action following a high HIV-risk needlestick injury was surprisingly poor. Only one third of all anaesthetists questioned appreciated the true risk of seroconversion following a high HIV risk needlestick injury, with 43% underestimating the risk. Less than half of all anaesthetists correctly identified high-risk body fluids, with consultant grades, whom may be advising trainee grades on appropriate action following needlestick injury, having significantly less knowledge than trainees. Other high risk fluids for the transmission of HIV such as amniotic fluid, vaginal secretions, semen, pericardial fluid, and unfixed organs and tissues were not tested in the questionnaire since we felt that anaesthetists are not exposed routinely to these fluids in everyday practice. One third of anaesthetists did not know that correct action following a needlestick injury was to promote active bleeding of the wound and to wash the wound thoroughly with soap and running water. Of particular concern was the finding that only 15% of anaesthetists knew correctly that post-exposure prophylaxis should be commenced within 1 h of the needlestick injury.

Anaesthetists are at risk of needlestick injuries, frequently handling needles and other sharp implements with potentially infected blood or CSF contamination. The rate of (unprotected) skin contact with blood has been estimated to be 18% for peripheral i.v. cannulation, 18% for insertion of a central venous catheter, and 85% for arterial cannulation.[7] A recent US study found that the rate of anaesthetists reporting a contaminated needlestick injury was 1.34 per 1000 anaesthetics performed.[4] A recently published study investigated surgeons with respect to their knowledge of post-exposure prophylaxis.[8] They found that 10 of the 26 surgeons questioned knew that post-exposure prophylaxis should be obtained within 1 h of the injury Interestingly only two out of the 26 knew where to obtain post-exposure prophylaxis outside of normal working hours.

Although we specifically studied anaesthetists' awareness of needlestick guidelines, there may be circumstances where high-risk fluids come into contact with broken skin or mucous membranes. In these situations post-exposure prophylaxis may be appropriate and further advice should be obtained from the specialists in occupational health medicine, ideally, again, within 1 h of the time of exposure. The risk of seroconversion from this type of contact with HIV infected fluid has been estimated as less than one in 1000 exposures.

In view of the active needlestick management policy and education programmes in this trust, and the medical background of the subjects, we were surprised that the knowledge amongst anaesthetists was so poor. This population may well be putting themselves at unnecessary risk of seroconversion to HIV both by failing to appreciate the risks of the body fluids they are handling and by not recognizing the need in high-risk cases to receive post-exposure prophylaxis within 1 h of injury. Current guidance from the Association of Anaesthetists entitled 'HIV and other blood borne viruses–guidance for anaesthetists'[9] was published prior to recommendations regarding post-exposure prophylaxis. The Royal College of Anaesthetists' FRCA examinations syllabus[10] does however require a knowledge of 'precautions in the management of the infective patient (e.g. HBV, HIV)' and 'implications for the anaesthetist of HIV infection'. Perhaps more emphasis on personal actions following needlestick injury is required.

The risk of exposure to potentially infected body fluids may be minimized by adherence to a policy of universal precautions. This includes the wearing of disposable gloves, using eye protection where appropriate, avoiding re-sheathing needles, not passing needles directly to another person, ensuring that all sharps are placed in disposal bins and regarding blood and the other high-risk fluids from any patient as potentially infected.[11]

The ignorance of post-exposure prophylaxis guidelines is likely to be similar amongst anaesthetists in other hospitals and probably other healthcare workers. Since timely post-exposure prophylaxis after high risk needlestick injuries is thought to reduce the risk of HIV seroconversion, we believe that many healthcare professionals may be putting themselves at increased risk of seroconversion after an HIV infected needlestick injury as a result of delay. Further dissemination of knowledge regarding high-risk fluids, risks from needlestick injury and appropriate action following a high HIV-risk needlestick injury is required. With the introduction of clinical governance, we believe that this issue is of priority in terms of risk management, teaching and continuing professional development.

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References

1 Berry AJ, Greene ES. The risk of needlestick injuries and needlestick-transmitted diseases in the practice of anesthesiology. *Anesthesiology* 1992; **77**: 1007–21

2 Marcus R. Surveillance of health care workers exposed to blood from patients infected with the human immunodeficiency virus *New Eng J Med* 1988; **319**: 1118–23

3 Tokars JI, Marcus R, Culver DH. Surveillance of HIV infection and zidovudine use among health care workers after occupational exposure to HIV-infected blood. *Ann Int Med* 1993, **118** 913–9

4 Greene ES, Berry AJ, Jagger J, Hanley E, Arnold WP, Bailey MK, *et al.* Multicenter study of contaminated percutaneous injuries in anesthesia personnel. *Anesthesiololgy* 1998; **89**: 1362–72

5 *Guidelines on Post-Exposure Prophylaxis for Health Care Workers Occupationally Exposed to HIV.* Department of Health, London, 1997

6 Tait AR, Tuttle DB. Prevention of occupational transmission of human immunodeficiency virus and hepatitis B virus among anesthesiologists: a survey of anesthesiology practice. *Anesth Analg* 1994; **79**: 623–8

7 Kristensen MS, Sloth E, Jensen TK. Relationship between anesthetic procedure and contact of anesthesia personnel with patient body fluids. *Anesthesiology* 1990; **73**: 619–24

8 Duff SE, Wong CKM, May RE. Surgeons' and occupational health departments' awareness of guidelines on post-exposure prophylaxis for staff exposed to HIV: a telephone survey. *BMJ* 1999; **319**: 162–3

9 *A Report Received by the Council of the Association of Anaesthetists on Blood Borne Viruses and Anaesthesia—an Update.* The Association of Anaesthetists of Great Britain and Ireland. London, 1996

10 *FRCA Syllabus.* Royal College of Anaesthetists. London 1999

11 Jeffries DJ. HIV and hepatitis—some way to go. *Anaesthesia* 1992; **47**: 921–2

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BJA

LABORATORY INVESTIGATIONS

Effects of propofol on functional activities of hepatic and extrahepatic conjugation enzyme systems

T. L. Chen[1]*, C. H. Wu[1], T. G. Chen[1], Y. T. Tai[1], H. C. Chang[1] and C. J. Lin[2]

[1]Department of Anaesthesia, Wan-Fang Hospital, Department of Surgery, Taipei Medical College, Taipei and [2]Department of Anaesthesia, College of Medicine, National Taiwan University, Taipei, Taiwan

**Corresponding author: Department of Anaesthesia, Taipei Medical College, Wan-Fang Hospital, No. 111, Sec. 3, Hsing-Lung Rd., Taipei, 116, Taiwan*

The effect of propofol on the hepatic and extrahepatic conjugation enzyme systems was assessed *in vitro* using microsomal and cytosolic preparations of human liver, hamster kidney, lung and gut. The functional activities of phase-II enzymes, including uridine diphosphate-glucuronosyltransferase (UDPGT), glutathione *S*-transferase (GST) and *N*-acetyltransferase (NAT) were evaluated in the presence of various concentrations of propofol (0.05–1.0 mmol litre^{-1}), using 1-naphthol, 1-chloro-2,4-dinitrobenzene and *p*-aminobenzoic acid as substrates respectively. Propofol produced concentration-dependent inhibition of UDPGT activity in human liver microsomes. Propofol did not produce significant inhibition of human hepatic GST activity at concentrations below 1.0 mmol litre^{-1}. In contrast, NAT activity was unaffected by propofol 0.05–1.0 mmol litre^{-1} in human liver cytosolic preparations. In extrahepatic tissues, hamster renal and intestinal UDPGT activities were significantly inhibited by propofol at 0.25–1.0 mmol litre^{-1}. In these tissues, GST and NAT were unaffected by propofol at 1.0 mmol litre^{-1}. Propofol produced differential inhibition of human liver and hamster extrahepatic conjugation enzymes as a result of different substrate and tissue specificities. The potential interference of the metabolic profile of phase-II enzymes as a result of inhibition by propofol (especially of UDPGT and GST) should be considered when using propofol with other drugs for anaesthesia.

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The principal metabolic reactions occurring in hepatic and extrahepatic tissues are classified into 'phase I', (including oxidation, reduction and hydrolysis) and 'phase II' (i.e. the conjugation pathways).[1–3] Phase-II drug metabolism is carried out by conjugation of drugs or their metabolites with endogenous compounds such as glucuronic acid, glutathione and acetate to convert hydrophobic compounds to hydrophilic compounds and to facilitate their elimination from the body.[4–6] Glucuronidation, for example, being one of the major conjugation reactions, is the key step involved in the metabolism of anaesthetics such as morphine, meperidine, codeine and the benzodiazepines.[7 8] The functions of these phase-II enzymes are known to be impaired in patients with severe liver disease or acute-phase responses such as inflammation.[9 10] Other factors, including sex, age, fasting and the ingestion of ethanol, may also regulate the function of phase-II enzyme systems.[11–13]

Propofol (2,6-diisopropylphenol) is a rapid-onset, short-acting intravenous anaesthetic agent that is used widely for the induction and maintenance of anaesthesia as well as for long-term sedation in intensive care units.[14 15] It has been noted that there is a pharmacokinetic interaction of propofol with narcotics, such as fentanyl and sufentanil, via inhibition of hepatic microsomal degradation.[16] Previous investigations have demonstrated that propofol interferes with the metabolism of co-administered drugs via animal and human liver phase-I metabolizing enzymes. For example, there is interference with cytochrome P450-dependent monooxygenases via interaction with the haemoprotein, and reduction of the efficiency of electron transport.[17 18] Whether the interactions caused by propofol occur purely via the phase-I enzymes or via phase-I and/or phase-II enzymes has not been examined. There are several lines

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of evidence indicating that propofol induces subclinical and reversible disturbance in hepatocellular integrity by affecting the serum level of hepatic transferase (conjugation) enzymes *in vivo* after long-term infusion.[19 20] The exact effect of propofol on the functional activities of specific phase-II conjugation enzymes has not yet been investigated. The aim of this study is to characterize the *in vitro* concentration–response effect of propofol on the metabolic function of various conjugation enzymes in both hepatic and extrahepatic tissues and to demonstrate the potential drug interactions involved in these metabolic pathways and clinical situations.

Materials and methods

Specimens and animal preparations

The study was approved by the National Science Council of Taiwan. After obtaining informed consent and local ethics committee approval, human liver specimens were obtained from six men and two women aged between 32 and 56 yr (mean 39 yr). Two of the specimens were obtained from organ donation for transplantation, and the other six were obtained as wedge biopsies from patients with intestinal pathology, none of whom had a history of liver disease or medication potentially affecting liver function. Exclusion criteria included liver function abnormalities such as abnormal serum levels of bilirubin (normal range 0–1.2 mg litre^{-1}), glutamic oxaloacetic transaminase (normal range 15–37 u litre^{-1}), glutamic pyruvic transaminase (normal range 15–45 u litre^{-1}) and lactate dehydrogenase (normal range 100–190 u litre^{-1}) as well as any histopathological abnormality. All liver tissues were freshly frozen in liquid nitrogen and stored at −80°C within 10 min of resection. Male Syrian hamsters, 10–12 weeks old, weighing 100–120 g, were purchased from the Animal Center of the College of Medicine (National Taiwan University, Taipei, Taiwan). They were housed and stabilized in a light-controlled environment with a 12-h light period for at least 1 week before being killed by decapitation. Kidneys, lungs and intestinal mucosa were removed, rinsed and homogenized in ice-chilled 1.15% KCl (w/v) solution. After differential centrifugation, cytosolic fractions and washed microsomes were prepared separately from homogenized tissues as described by Alvares and Mannering.[21] Microsomes from the kidneys, lungs and gut were pooled from four animals and frozen at -70°C; the pellets were resuspended in potassium phosphate buffer 0.1 mol litre^{-1} at pH 7.4 for assay. Microsomal and cytosolic proteins were assayed by the method of Lowry using bovine serum albumin as standard.[22]

Phase-II enzyme assays

Pure propofol (ICI Pharmaceutica, Zeneca, Macclesfield, UK) was diluted in microsomal and cytosolic fractions of homogenized tissues. Concentration–response effects of propofol (0.05–1.0 mmol litre^{-1}) for each enzyme assay were evaluated in human liver and hamster renal, lung and gut tissues, and compared with the control.

UDP-glucuronosyltransferase assay

Uridine diphosphate-glucuronosyltransferase (UDPGT) activity was studied by the method of Mackenzie and Hanninen, using 1-naphthol as the substrate.[23] In brief, the enzymic reaction was initiated by mixing various concentrations of propofol and 50% microsomes with 20 mg ml^{-1} sodium cholate (1:1 v:v) and cooling on ice for 30 min. The pretreated microsomal preparation was added to K-PO_4 buffer 50 mmol litre^{-1}, $MgCl_2$ 0.1 mol litre^{-1} and 1-naphthol 4.17 mmol litre^{-1} and incubated in 37°C for 5 min. After adding UDP-glucuronic acid 5 mmol litre^{-1}, microsomal protein was incubated at 37°C for 10 min in the sample group, using K-PO_4 buffer 50 mmol litre^{-1} as blank. The reaction was stopped on ice after 5 min. The fluorescence intensity of the product, 1-naphthol β-D-glucuronide, was measured at excitation and emission wavelengths of 293 and 335 nm respectively.

Glutathione S-transferase assay

In this study, we carried out the glutathione *S*-transferase (GST) assay using the standard substrate 1-chloro-2,4-dinitrobenzene, following the procedure of Habig *et al.*[24] Essentially, the reaction mixture contained 1 mmol litre^{-1} glutathione in 0.1 mmol litre^{-1} K-PO_4 buffer with 1 mmol litre^{-1} EDTA. After addition of 1 mmol litre^{-1} 1-chloro-2,4-dinitrobenzene to the sample cuvette, the absorbance of the mixture was measured at 340 nm for the baseline, with methanol as a reference. Cytosolic protein in 0.1 mmol litre^{-1} K-PO_4 buffer, pH 6.5, preincubated with various concentrations of propofol, was then added to the mixture to start the reaction for 1 min. The rate of reaction was monitored by measuring the absorbance increased at 340 nm.

N-*acetyltransferase assay*

N-acetyltransferase (NAT) activity was measured by quantifying the disappearance of the arylamine substrate, as reflected by decreasing formation of Schiff base with dimethylaminobenzaldehyde.[25] In brief, the incubation system consisted of Tris–HCl 75 mmol litre^{-1}, pH 7.5, at 37°C, dithioerythreitol 1.5 mmol litre^{-1}, EDTA 1.5 mmol litre^{-1}, acetyl phosphate 22.5 mmol litre^{-1}, phosphotransferase 2.5 U ml^{-1}, *p*-aminobenzoic acid 0.4 mmol litre^{-1} in Tris–HCl buffer, and 50 μl of diluted cytosol preincubated with propofol. The reaction was started by the addition of 40 μl of acetyl coenzyme A 1 mmol litre^{-1} to the incubation mixture and was incubated at 37°C for 45 min. The reaction was terminated by the addition of 100 μl of 20% (w/v) tricyclic acid (TCA). The reaction mixture was centrifuged and the supernatant was mixed with 1 ml of 5% dimethylaminobenzaldehyde. The sample

Table 1 Functional activities of various phase-II drug-metabolizing enzymes in human liver, hamster kidney, lung and gut. All values are mean (SD) of *n* observations. Each hamster tissue sample was pooled from four animals

Assay	Human liver	Hamster		
		Kidney	Lung	Gut
n	8	6	6	6
Microsomal protein (mg g tissue^{-1})	35.8 (6.8)	4.62 (0.88)	3.91 (0.74)	3.60 (0.48)
Cytosolic protein (mg g tissue^{-1})	49.7 (4.6)	42.8 (3.9)	37.6 (9.6)	28.4 (3.9)
UDPGT (nmol min^{-1} mg protein $^{-1}$)	3.26 (0.75)	2.07 (0.38)	0.032 (0.004)	0.74 (0.12)
GST (nmol min^{-1} mg protein $^{-1}$)	2.16 (0.86)	1.64 (0.61)	0.64 (0.28)	0.61 (0.20)
NAT (nmol min^{-1} mg protein $^{-1}$)	7.06 (0.67)	2.17 (0.37)	0.87 (0.34)	3.04 (0.98)

was recentrifuged and incubated for at least 10 min at room temperature, and the absorbance at 450 nm was then recorded.

Unless otherwise stated, all results are presented as mean (SD). Data were analysed using one- and two-way analyses of variance and significant differences between concentrations were identified using the Student–Newman–Keuls test or the unpaired *t*-test. $P<0.05$ was considered statistically significant.

Results

The activities of various enzymes were expressed on the basis of protein concentrations in the reaction mixture (Table 1). Protein content in the cytosolic components was consistently greater than in the microsomal fraction. Human liver exhibited the highest rate of catalytic activity. Enzyme activities in hamster lung tissues were lower than in the other tissues studied. Among the extrahepatic tissues, kidney contained the highest activity of UDPGT and GST, whereas the intestine contained the highest NAT activity. NAT showed the highest metabolic activity on a protein basis among all enzymes within all the tissues studied.

The effects of various concentrations of propofol on functional activities of specific phase-II enzymes evaluated within human liver microsomal and cytosolic fractions are shown in Figure 1. In human liver microsomes, propofol 0.05 mmol litre^{-1} produced a small but non-significant decrease in UDPGT activity ($P=0.08$). Between 0.10 and 1.0 mmol litre^{-1}, propofol demonstrated concentration-dependent inhibition of UDPGT activity. The metabolic rate of UDPGT in human microsomes was decreased to 50% of the control by propofol 0.10 mmol litre^{-1} ($P=0.026$) and to 14% of the control by propofol 1.0 mmol litre^{-1} ($P=0.0041$). The activity of GST was not significantly inhibited at low concentrations of propofol (0.10–0.5 mmol litre^{-1}), but was significantly inhibited at a high concentration of propofol (1.0 mmol litre^{-1}) ($P=0.032$). The metabolic rate of NAT in human liver was unaffected by propofol (Fig. 1).

Figure 2 summarizes the effects of propofol on the functional activities of various enzymes in hamster kidney, lung and gut. The specific enzyme activity per unit weight of protein in hamster kidney was about one- to two-thirds of the activity in human liver. Propofol 0.25–1.0 mmol litre^{-1} caused a 40–79% decline in hamster kidney UDPGT activity ($P<0.05$). Unlike the result obtained in human liver, the effect of propofol in hamster kidney was only a minor decline in GST activity, and this did not reach statistical significance ($P=0.12$ at propofol 1.0 mmol litre^{-1}). As in human liver, NAT activity was not influenced by increasing concentrations of propofol in hamster kidney (Fig. 2, top panel). In hamster lung tissues, the activities of GST and NAT were much lower than in human liver. The activity of UDGPT was just detectable in hamster lung. In contrast with kidney and gut, neither of the above enzymes in lung was affected by propofol (Fig. 2, middle panel). In gut, propofol 0.25–1.0 mmol litre^{-1} produced 35–70% inhibition of UDPGT activity ($P<0.05$). However, GST and NAT activities were unaffected (Fig. 2, bottom panel).

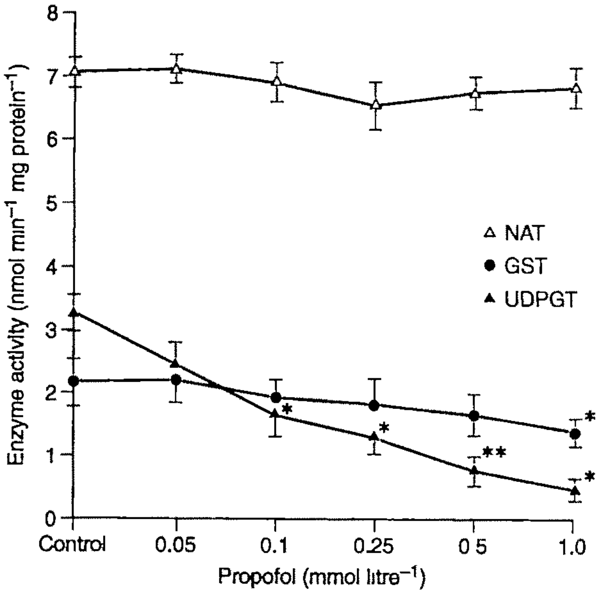

Fig 1 Effect of propofol concentration on the activities of UDPGT, GST and NAT in human liver microsomal and cytosolic preparations. Values are mean (±SEM) of three measurements in each enzyme assay ($n=8$). *$P<0.05$, **$P<0.01$ *vs* control (one-way ANOVA with *post hoc* Student–Newman–Keuls test)

Discussion

Traditionally, plasma levels of conjugation enzymes, such as GST, are important parameters for the assessment of

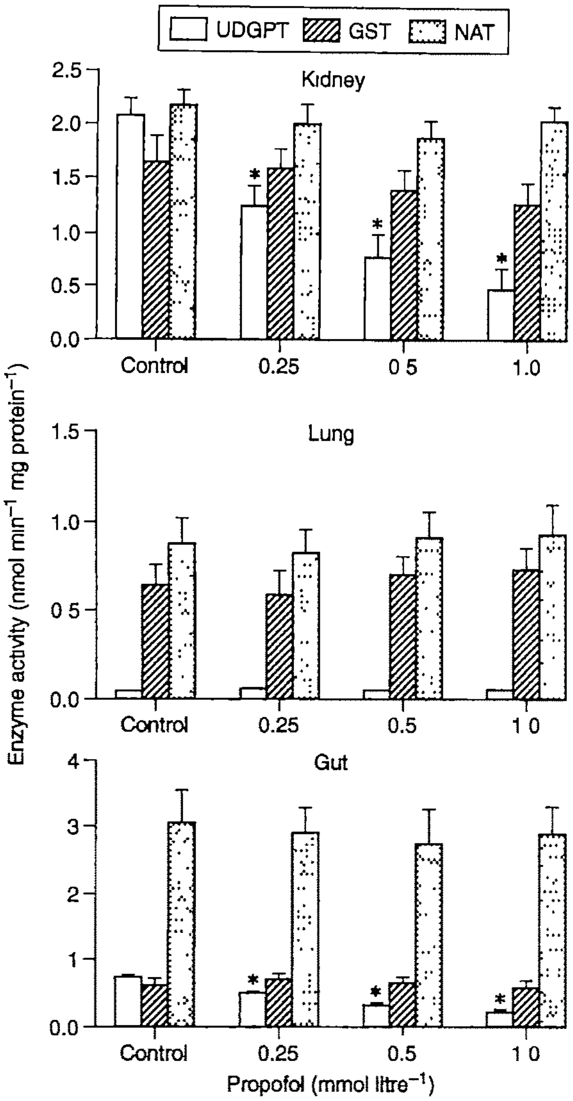

Fig 2 Effect of propofol concentration on the activities of UDPGT, GST and NAT in microsomal and cytosolic preparations of hamster kidney, lung and gut. Values are mean (SEM) of three measurements in each enzyme assay (n=6, each pooled from four animals). *P<0.05 *vs* control group (one-way ANOVA with *post hoc* Student–Newman–Keuls test).

hepatocellular injury. After exposure to general anaesthesia or long-term infusion of propofol, the plasma level of GST increases significantly, indicating the presence of hepatocellular damage and the leakage of cytosolic enzymes into the extracellular space.[5 19 20 26] UDPGTs, the most important phase-II enzymes we studied in the microsomal fraction, have a wide distribution in hepatic and extrahepatic tissues.[3 4] Clinically, the plasma concentrations of propofol in humans and the hamster have been reported to reach 0.067–0.10 mmol litre^{-1},[27–29] although this would be reduced by a high level of protein binding. Under similar concentrations *in vitro*, our data showed that propofol produced significant inhibition of the conjugation activities of human liver and hamster extrahepatic UDPGT. Concentration–response curves demonstrated concentration-dependent inhibition of UDPGT when we increased the concentration of propofol from 0.10 to 1.0 mmol litre^{-1}.[18 27–29] Many endogenous and exogenous amines, steroids and opioid compounds are metabolized through glucuronidation reactions by UDPGTs.[7] A previous investigation by Janicki *et al.* showed that the microsomal degradation of narcotics, such as alfentanil and sufentanil, was hindered by the presence of propofol.[16] Besides propofol's inhibition of microsomal monooxygenases, the inhibition of glucuronidation by propofol provides another possible mechanism for the interference of pharmacokinetics and drug interactions with opioids.[17 18 29]

Many factors have been studied and identified as modulators or inhibitors of UDPGT activity that might provide explanations of the above findings. UDPGT proteins are membrane proteins with a hydrophobic membrane-spanning domain at their carboxyl terminus in addition to other hydrophobic domains throughout the molecule, which probably function to bind hydrophobic molecules.[30 31] Propofol, a molecule with a high octanol/water partition coefficient, is suitable for hydrophobic binding with UDPGT proteins.[14] Also, phenol activity was shown to be dependent on the binding of phospholipids, and phospholipid binding leads to conformational changes in the UDPGT enzyme.[32] As an alkylated phenol, propofol might exhibit its potent inhibition of UDPGT through binding to the membrane protein and induce alterations in enzyme conformation as well as a reduction of its reactivity.[14] The present analysis of extrahepatic tissues in the hamster also showed that the gut and the kidneys are another two important sites for glucuronidation; only modest activity was observed in the lungs. Propofol at 0.25–1.0 mmol litre^{-1} exhibited similar, but lower, inhibition of UPDGT activity in hamster kidney and gut than in human liver. The difference between the hepatic and extrahepatic effects of propofol on UDPGT might be attributable to the species- and tissue-specificity of the enzyme.[3 4] The tissue distribution of the enzyme and the functional heterogeneity of the UDPGT enzyme family within different tissues might explain the differences in the inhibition induced by propofol.[4]

The GSTs are also a complex multigene family of enzymes that are widely distributed in various tissues.[33] These enzymes are primarily located in the cytosol and are important in detoxification by conjugating reduced glutathione with a large number of electrophiles.[34] The plasma level GST has been used as a sensitive indicator of hepatocellular integrity in liver diseases or liver damage induced by drug intoxication.[5 35 36] Our data showed that propofol did not exhibit significant inhibition of GST activity at concentrations less than 1.0 mmol litre^{-1}. There are several possible explanations. First, the present study showed that GST activity was relatively low among these phase-II enzymes in human liver, hamster kidney and gut tissues, making significant inhibition more difficult to detect. Secondly, GST may bind a number of anions, such as bile salts, which might inhibit enzymic activity.[37] Being a phenolic substitute, propofol might participate in the conjugation reactions as a hydrogen provider (functional anion) and bind with GST to reduce its conjugating ability.[14] This might explain why propofol produced inhibition of GST only at high concentrations. GST in hamster extrahepatic tissues was essentially unaffected by propofol. The discrepancy in propofol's inhibiting effect between hepatic and extrahepatic tissues might result from functional heterogeneity of the distribution of various GST isoenzymes within different species and tissues.[38] It is possible that GSTs serve different functions in different tissues, sometimes acting as carrier proteins rather than being metabolically active.[5]

N-acetylation is another important phase-II conjugation reaction, and NATs are responsible for the metabolism of a large number of drugs and compounds, including isoniazid, hydralazine, procainamide, caffeine and arylamine carcinogens.[39] Previous studies have shown that the effects of liver diseases on acetylation seem to be modest and of lesser magnitude than their effects on oxidative pathways.[69] In our data, NAT exhibited the highest activity among these phase-II enzymes. NAT activity in the intestine is about one-half that in liver, 50% higher than that in kidney and three times that in lung, so that the gut is also an important site of acetylation. In contrast to other phase-II enzymes, propofol produced no significant inhibition of NAT activity in either hepatic or extrahepatic tissues. Compared with UDPGT and GST, NAT is less polymorphic in terms of isoenzymes and tissue-specificity.[6] The substrate for the measurement of NAT activity, *p*-aminobenzoic acid, is also different from propofol in physicochemical properties, indicating that interaction of propofol with NAT is clinically irrelevant.[3]

Clinically, the mechanisms involved in the interactions of drugs with propofol might be multifactorial. First, the haemodynamic alterations caused by propofol might reduce the regional blood flow as well as the regional delivery of agents to the sites of metabolism.[40 41] Therefore, it is likely that the tissue uptake and elimination of the coadministered drugs would be modified.[40 41] Secondly, propofol might compete for serum protein binding, which might increase the free fraction and probably potentiate the pharmacodynamic effects of other drugs, such as propranolol.[42] Thirdly, in our previous studies propofol exhibited broad-spectrum, concentration-dependent inhibition of cytochrome P450-dependent monooxygenases (phase-I enzymes). Propofol 0.05–0.10 mmol litre^{-1} showed significant inhibition of cytochrome P450 2E1, 1A1 and 2B1, which might hinder the metabolism of coadministered drugs.[17 18] The present study demonstrated that propofol was also able to inhibit the conjugation enzymes to various degrees at similar concentrations. The interference with these phase-II enzymes by propofol complicated the pharmacokinetics, and clinicians should be aware of potential propofol-related drug interactions during anaesthetic practice.

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References

1 Guengerich FP. Reaction and significance of cytochrome P-450 enzymes. *J Biol Chem* 1991; **266**: 10019–22

2 Pacifici GM, Franchi M, Bencini C, Repetti F, Lascio ND, Muraro GB. Tissue distribution of drug-metabolizing enzyme in humans. *Xenobiotica* 1988; **18**: 849–56

3 Gram TE, Okine LK, Gram RA. The metabolism of xenobiotics by certain extrahepatic organs and its relation to toxicity. *Annu Rev Pharmacol Toxicol* 1986; **26**: 259–91

4 Tephly TR, Green MD, Coffman BL, King C, Cheng Z, Rios GR. Metabolism of endobiotics and xenobiotics by UDP-glucuronosyltransferase. *Adv Pharmacol* 1998; **42**: 343–6

5 Hayes PC, Bouchier IAD, Beckett GJ. Glutathione S-transferase in humans in health and disease. *Gut* 1991; **32**: 813–8

6 Levy M, Caraco Y, Geisslinger G. Drug acetylation in liver disease. *Clin Pharmacokinet* 1998; **34**: 219–26

7 Coffman BL, Rios GR, Tephly TR. Purification and properties of two rat liver phenobarbital-inducible UDP-glucuronosyltransferases that catalyzes the glucuronidation of opioids. *Drug Metab Dispos* 1996; **24**: 329–33

8 Gerkens JF, Desmond PV, Schenker S, Branch RA. Hepatic and extrahepatic glucuronidation of lorazepam in the dog. *Hepatology* 1981; **1**: 329–35

9 Hoyumpa AM, Schenker S. Is glucuronidation truly preserved in patients with liver disease? *Hepatology* 1991; **13**: 786–95

10 Strasser SI, Mashford ML, Desmond PV. Regulation of uridine diphosphate glucuronosyltransferase during the acute-phase response. *J Gastroen Hepatol* 1998; **13**: 88–94

11 Zaphiropoulos PG, Mode A, Norstedt G, Gustaffson JA. Regulation of sexual differentiation in drug and steroid metabolism *Trends Pharmacol Sci* 1989; **10**: 149–53

12 Wynne HA, James OFW. The aging liver. *Age Ageing* 1990, **19**: 1–3

13 Hoyumpa AM, Schenker S. Major drug interactions: effect of liver disease, alcohol and malnutrition. *Annu Rev Med* 1983; **33**: 113–49

14 Deegan RJ. Propofol: a review of the pharmacology and applications of an intravenous anesthetic agent. *Am J Med Sci* 1992; **304**: 45–9

15 Bailie GR, Cockshott ID, Douglas EJ, Bowles BJM. Pharmacokinetics of propofol during and after long term continuous infusion for maintenance of sedation in ICU patients. *Br J Anaesth* 1992; **68**: 486–91

16 Janicki PK, James MFM, Erskine WAR. Propofol inhibits enzymatic degradation of alfentanil and sufentanil by isolated liver microsomes in vitro. *Br J Anaesth* 1992; **68**: 311–2

17 Baker MT, Chadam MV, Ronnenberg WC Jr. Inhibitory effects of propofol on cytochrome P450 activities in rat hepatic microsomes. *Anesth Analg* 1993; **76**: 817–21

18 Chen TL, Ueng TH, Chen SH, Lee PH, Fan SZ, Liu CC. Human cytochrome P450 monooxygenase system is suppressed by propofol. *Br J Anaesth* 1995; **74**: 558–62

19 Tiainen P, Lindgren L, Rosenberg PH. Disturbance of hepatocellular integrity associated with propofol anaesthesia in surgical patients. *Acta Anaesthesiol Scand* 1995; **39**: 840–4

20 Motsch J, Schmidt H, Bach A, Bottiger BW, Bohrer H. Long-term sedation with propofol and green discolouration of the liver. *Eur J Anaesth* 1994; **11**: 499–502

21 Alvares AP, Mannering GJ. Two-substrate kinetics of drug-metabolizing enzyme systems of hepatic microsomes. *Mol Pharmacol* 1970; **6**: 206–11

22 Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with Folin phenol reagent. *J Biol Chem* 1951; **193**: 265–75

23 Mackenzie PI, Hanninen O. A sensitive kinetics assay for UDP-glucuronosyltransferase using 1-naphthol as substrate. *Anal Biochem* 1980; **109**: 362–8

24 Habig WH, Pabst MJ, Jacoby WB. Glutathione S-transferase. The first enzymatic step in mercapturic acid formation. *J Biol Chem* 1974; **249**: 7130–9

25 Anders HH, Klem AJ, Szabo SM, Weber WW. New spectrophotometric and radiochemical assays for acetyl-CoA: arylamine N-acetyltransferase applicable to a variety of arylamines. *Anal Biochem* 1985; **145**: 367–75

26 Hussey AJ, Howie J, Allan LG, Drummond G, Hayes JD, Beckett GJ. Impaired hepatocellular integrity during general anaesthesia, as assessed by measurement of plasma glutathione S-transferase. *Clin Chim Acta* 1986; **161**: 19–28

27 Kantos J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. *Clin Pharmacol* 1989; **17**: 308–26

28 Lange H, Stephan H, Rieke H, Kellermann M, Sonntag H, Bircher J. Hepatic and extrahepatic disposition of propofol in patients undergoing coronary bypass surgery. *Br J Anaesth* 1990; **64**: 563–70

29 Chen TL, Wang MJ, Huang CH, Liu CC, Ueng TH. Difference between *in vivo* and *in vitro* effects of propofol on defluorination and metabolic activities of hamster hepatic cytochrome P450-dependent mono-oxygenases. *Br J Anaesth* 1995; **75**: 462–6

30 King C, Green MD, Rios GR, *et al.* The glucuronidation of exogenous and endogenous compounds by stably expressed rat and human UDP-glucuronosyltransferase 1.1. *Arch Biochem Biophys* 1996; **232**: 92–100

31 Mackenzie PI, Owen IS, Burchell B, *et al.* The UDP glycosyltransferase gene superfamily: recommended nomenclature update based on evolutionary divergence. *Pharmacogenetics* 1997; **7**: 255–69

32 Singh OMP, Graham AB, Wood GC. The phospholipid dependence of UDP-glucuronosyltransferase: conformation/reactivity studies with purified enzyme. *Biochem Biophys Res Commun* 1982; **107**: 345–9

33 Mannervik B. The isoenzymes of glutathione transferase. *Enzymol Relat Areas Mol Biol* 1980; **57**: 357–417

34 Wolkoff AW. The glutathione S-transferases: their role in the transport of organic anions from blood to bile. *Int Rev Physiol* 1980; **21**: 151–69

35 Mulder TPJ, Janssens AR, de Bruin WCC, Peters WHM, Cooreman MP, Jansen JBMJ. Plasma glutathione S-transferase alpha-1 levels in patients with chronic liver disorders. *Clin Chim Acta* 1997; **258**: 69–77

36 Beckett GJ, Chapman BJ, Dyson EH, Hayes JD. Plasma glutathione S-transferase measurements after paracetamol overdose: evidence for early hepatocellular damage. *Gut* 1985; **26**: 26–31

37 Singh SV, Leal T, Awasthi Y. Inhibition of human glutathione S-transferase by bile acids. *Toxicol Appl Pharmacol* 1980; **95**: 248–54

38 Hayes PC, Harrison DJ, Bouchier IAD, McLellan LI, Hayes JD. Cytosolic and microsomal glutathione S-transferase isoenzymes in normal human liver and intestinal epithelium. *Gut* 1989; **30**: 854–9

39 Weber WW, Hein DW. N-acetylation pharmacogenetics. *Pharmacol Rev* 1985; **37**: 25–79

40 Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia and maintained with propofol. *Br J Anaesth* 1988; **60**: 3–9

41 Runciman WB, Mather LE, Selby DG. Cardiovascular effects of propofol and of thiopentone anaesthesia in the sheep. *Br J Anaesth* 1990; **65**: 353–9

42 Perry SM, Whelan E, Shay S, Wood AJJ, Wood M. Effects of i.v. anaesthesia with propofol on drug distribution and metabolism in the dog. *Br J Anaesth* 1991; **66**: 66–72

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Vagally mediated sympathoexcitation and central depression by desflurane in rabbits

C. K. Pac-Soo[1] *, C. Wang, D. Ma, M. K. Chakrabarti and J. G. Whitwam

Department of Anaesthetics and Intensive Care, Imperial College School of Medicine, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

[1]Present address: Department of Anaesthetics, Wycombe Hospital, Queen Alexandra Road, Buckinghamshire HP11 2TT, UK

**Corresponding author*

The effects of desflurane on renal sympathetic nerve activity (RSNA) were studied in intact or vagotomized anaesthetized rabbits with initial concentrations of 4.5–18%, subsequently equilibrated to end-tidal concentrations from 3%, 6%, 9% and 12% each for 20 min allowing sympathetic activity to stabilize. In intact animals, immediate transient increases in mean sympathetic activity from 27% to 63% were closely related to initial concentrations from 4.5% to 18%. During subsequent equilibration this remained elevated by 25–30% up to 6%, returned to control at 9% and fell by 33% at 12%. Bilateral vagotomy abolished sympathoexcitation apart from small increases in sympathetic activity, for example 14% at 4.5% ($P<0.05$). We conclude that increases in inspired desflurane concentrations evoked rapid transient vagally mediated reflex sympathoexcitation with a small extra-vagal contribution. Central depression of sympathetic activity started at 6% and was 33% below baseline at 12%.

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The mechanisms underlying sympathoexcitation in response to increases in desflurane concentrations have yet to be determined.[1–5] Baroreflexes are not a major contributory factor as sympathoexcitation is the same when hypotension is prevented with vasoconstrictor drugs.[5 6] Desflurane also causes immediate excitatory phenomena, for example coughing, which could indicate that a rise in spontaneous sympathetic activity is due to stimulation of 'irritant receptors' in the airways.[7–10] It has also been stated that repeated exposure of human volunteers to desflurane is associated with a progressive reduction in sympathetic responses,[11] which could be due to rapid adaptation of such 'airway receptors'.[12 13] However, other workers have found that topical anaesthesia of the airways and local block of their innervation do not suppress sympathoexcitation,[14] which could indicate primary involvement of deeper structures in the lungs or other tissues.

The present study, in rabbits, tested the hypothesis that the increase in sympathetic activity caused by desflurane is due to reflexes mediated by afferent fibres in the vagus nerves and that higher concentrations which cause sympathetic depression do so by a direct effect on the central nervous system.

Materials and methods

General procedures

The study was approved by the UK home office (licence PLL 90/00852). Ten New Zealand rabbits of both sexes (3.1–4.2 kg) were anaesthetized with a single bolus sleep dose of methohexitone 15–20 mg kg^{-1} and then maintained with 1% α-chloralose using an initial bolus of 30 mg kg^{-1} followed by an infusion of 17–20 mg kg^{-1} h^{-1}. A tracheostomy was performed several rings below the cricoid cartilage and a 3.5-mm tube was inserted into the trachea with a ligature tied around the trachea. This was done to stop a gas leak, and hence to control blood-gas tensions, and to prevent desflurane from reaching the upper airways. The lungs were mechanically ventilated (SLE 2000, SLE, Surrey, UK) through the tracheotomy tube at 30 b.p.m. with oxygen-enriched air. Muscle paralysis was maintained with bolus doses of succinylcholine (2 mg kg^{-1} i.v.) every 30 min. The depth of anaesthesia was assessed by floppy ears and absence of a glabellar reflex and spontaneous muscle movement, when succinylcholine was temporarily withheld at intervals of ~90 min to allow the return of muscle tone and ensure continuity of anaesthesia. A femoral artery and vein were cannulated for direct arterial pressure measurement and

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the infusion of α-chloralose, respectively. Oesophageal temperature was measured with a thermistor (Yellow Springs Instruments, OH, USA) and was maintained between 37 and 38°C. At regular intervals and at the beginning and end of the collection of each data set pHa, Pa_{CO_2} and Pa_{O_2} were measured with a blood-gas analyser (ABL3, Radiometer, Copenhagen, Denmark) and the values maintained between 7.35 and 7.40, 35 and 39 mm Hg, and 180 and 200 mm Hg, respectively. Mean arterial pressure (MAP) and heart rate (HR) were recorded continuously (MacLab 8 ADInstruments, ADInstruments Pty, Australia).

The animals were randomly divided into two groups. In five rabbits the vagus nerves were intact and in the other five they were divided. Each preparation was allowed to stabilize for 30 min after surgery before baseline data were recorded.

Recording of sympathetic nerve activity

The right kidney was exposed retroperitoneally and a single fascicle of the renal sympathetic nerve was dissected from the surrounding tissues, desheathed cut distally, and mounted on silver electrodes in a pool of warm mineral oil. Signals were pre-amplified (Tectronix 122, Tectronix, Beaverton, OR, USA) and displayed on an oscilloscope (Tectronix 565, Tectronix). To compare renal sympathetic nerve activity at various stages of the study, 20-s periods of a continuous multifibre recording were subjected to full-wave rectification and integrated with a time constant of 100 ms (NL90, Neurolog, Welwyn Garden City, UK). Both direct and integrated signals were displayed on an oscilloscope and plotted with a thermal recorder (Gould 1602 system, Gould, Essex, UK). The total mean electrical activity was processed as the average of the areas within three envelopes of integrated spontaneous sympathetic activity expressed in arbitrary units, and hence as a percentage of control values at each stage of the study.

Vagotomy

In five of the preparations, both vagus nerves were exposed in the neck, adjacent to the carotid arteries and above the level of the tracheostomy. A short section was dissected free from surrounding tissues and loose ligatures were placed around the nerves. After control recordings of sympathetic activity, MAP and HR were processed, both vagus nerves were cut between the ligatures to prevent bleeding. The effects on sympathetic activity and the resting circulation were observed, and 30 min were allowed for possible post-injury discharges in the proximal part of the vagus nerves to decline. Further observations were then recorded which became the control data for the effects of desflurane after vagotomy.

Each preparation was allowed to stabilize for 30 min after surgery before control data were recorded. Stability of the preparations was ensured by an absence of changes in both electrophysiological and haemodynamic data before starting each study. The second data set was used as control.

Administration of desflurane and experimental protocol

Desflurane was delivered from a heated vaporizer Tec 6 (Ohmeda, West Yorkshire, UK). The end-tidal concentration of desflurane was measured at the proximal end of the tracheal tube, with an infrared analyser (Capnomac III, Datex, Helsinki, Finland). The gas analyser was calibrated with commercially available standard gases (Quick Cal™, Datex, Helsinki, Finland).

At each concentration, overpressure was used to achieve rapid equilibration and the vaporizer was initially set to deliver a desflurane concentration 1.5 times greater than the final target equilibrated end-tidal concentration. The concentration was progressively reduced maintaining the expired concentration constant at the target level until equilibration was achieved after which no further reductions in the inspired concentrations were required. A total of 20 min administration was more than required to achieve a new stable level of sympathetic activity, HR and arterial pressure. Desflurane was administered continuously at concentrations from 4.5%, 9%, 13.5% and 18% to achieve equilibrated end-tidal concentrations of 3%, 6%, 9% and 12%, respectively. Sympathetic activity was recorded at 1, 3, 5, 10, 15 and 20 min after the concentration changes. Finally it was withdrawn and the preparations allowed to recover with a return to control values for sympathetic activity and MAP.

Statistics

Within each group, the data were analysed using ANOVA for repeated measurements followed by *t*-tests with Bonferroni correction when appropriate. A value of $P<0.05$ was considered significant.

Results

There were no significant differences in baseline HR, MAP, sympathetic activity between the vagotomized and intact vagus group of animals.

Spontaneous renal sympathetic activity

Figure 1 shows a typical recording of the responses in sympathetic activity to increases in desflurane concentrations in one intact rabbit.

Intact group

Rapid changes in inspired desflurane concentrations to 4.5%, 9%, 13.5% and 18% caused immediate increases in RSNA, at 1 min, to 127(14)%, 142(18)%, 150(25)% and 163(35)% of baseline, respectively, $P<0.05$, which were concentration dependent (Fig. 2A). After equilibration at 3% and 6%, sympathetic activity was maintained at ~25–30% above baseline, $P<0.05$. In contrast, at 9% it returned to baseline and then progressively depressed to 67(26)% of baseline at 12%, $P<0.05$. Thus, for the equilibrated 20 min concentration with the vagus nerves intact, the overall effect on sympathetic

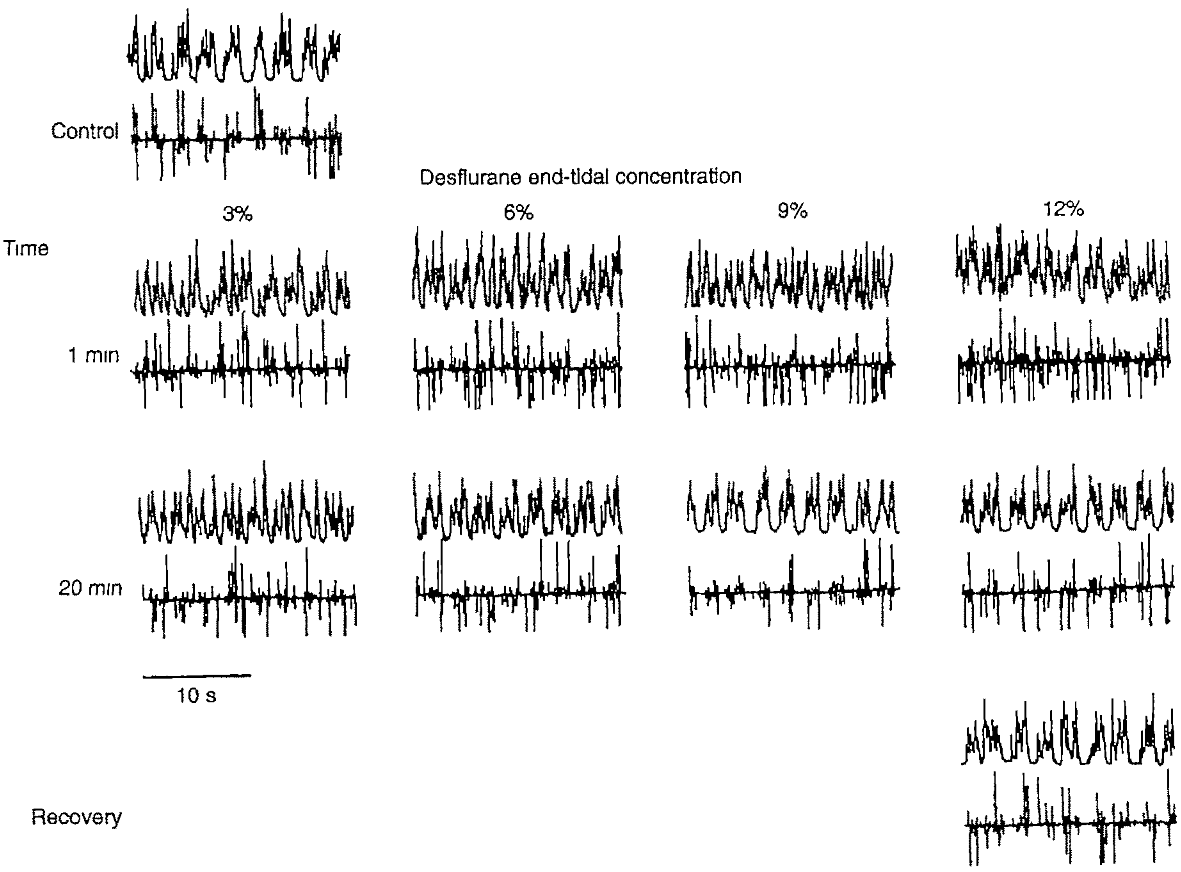

Fig 1 Typical recording of spontaneous renal sympathetic nerve activity (RSNA) following rapid increases in desflurane concentration during 20 s periods in intact rabbits Traces show recording at control, 1 min and 20 min after each new vaporizer setting, and after withdrawal of desflurane In each panel, lower trace=direct amplified recording of RSNA, upper trace=rectified integrated signals for quantitative comparison.

activity was biphasic, with sustained activity around 29% above baseline up to 6% and subsequent depression of 33% at 12% concentration.

Vagotomy group

At equilibrated concentrations, we observed a progressive decrease in sympathetic activity which became statistically significant to 67(24)% and 57(22)% of control at 9% and 12%, respectively ($P<0.05$). Thus, there was no evidence of a vagally mediated increase in sympathetic activity that could be due to excitation at equilibrated concentrations. However, at the first introduction of desflurane, for example at 4.5% there was a statistically significant increase in sympathetic activity to 114(4)% of baseline ($P<0.05$). Thereafter at subsequent concentration changes there were small progressive increases in sympathetic activity, which did not reach statistical significance (Fig. 2B).

In both groups, recovery of sympathetic activity occurred within ~60 min.

Mean arterial pressure

Intact group

There was no significant change in MAP following the administration of desflurane up to an end-tidal concentration of 3% (Fig. 3). Thereafter, increasing concentrations produced progressive depression in MAP to 65(17) mm Hg, 49(14) mm Hg and 34(8) mm Hg at equilibrated end-tidal concentrations of 6%, 9% and 12%, respectively, from a control value of 79(15) mm Hg, $P<0.05$. MAP returned to baseline values within 60 min after withdrawal of desflurane.

Vagotomy group

Following vagotomy there was an increase of 8(5) mm Hg in MAP that was not statistically significant. Thereafter, increasing concentrations of desflurane caused similar reductions in MAP to the intact group, for example from the control value of 88(11) mm Hg to 41(10) mm Hg at an equilibrated concentration of 12%.

Heart rate

Vagotomy did not produce any significant change in HR (to 264(18) beats min^{-1}) from the pre-vagotomy baseline value (263(16) beats min^{-1}). Also there was no statistically significant change in HR from baseline values during the administration of desflurane in both groups.

Discussion

There is no doubt that desflurane causes excitation of the sympathetic nervous system,[1–3 14 15] but the mechanisms

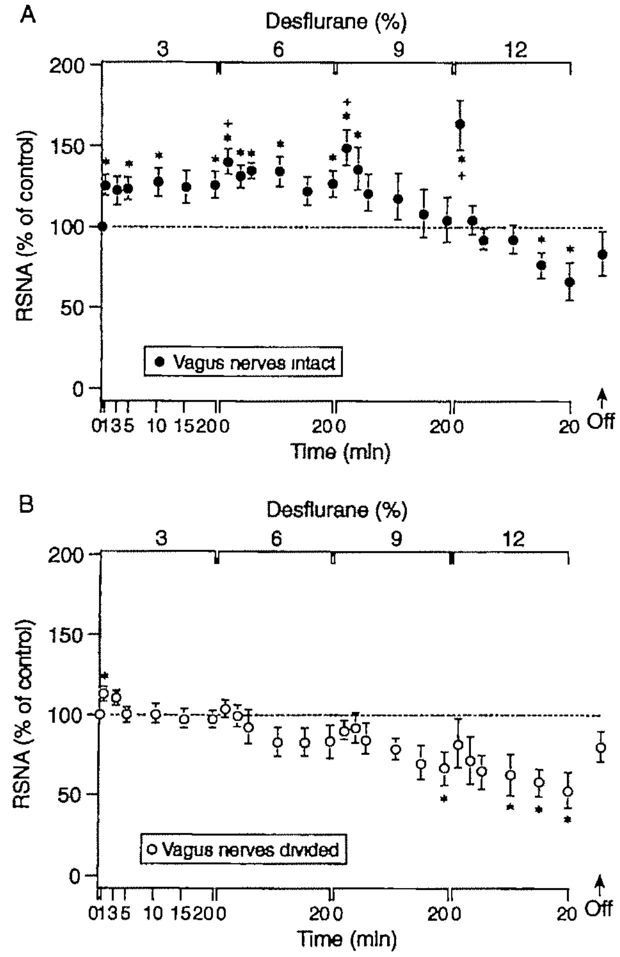

Fig 2 Summary of data from rectified and integrated signals of renal sympathetic nerve activity (RSNA) following rapid increases in desflurane concentrations in intact rabbits (A) and following bilateral vagotomy (B) Off indicates values after withdrawal of desflurane Values are expressed as per cent of control (mean (SD), $n=5$). Comparison with control: $*P<0.05$. Comparison between data at 20 min (preceding concentration) with those at 1 min at immediate higher concentration $+P<0.05$.

involved remain an area of critical debate.[5 6 9 14–18] Previous studies have been concerned only with sympathetic excitation and the circulation at concentrations of up to 1.5 MAC.[3 4 11 18] Hitherto only one study has described depression of sympathetic activity by desflurane which decreased by ~65% at a higher concentration of 12% in a dog model.[15]

Weiskopf and associates[3] speculated that the increase in sympathetic outflow caused by a rapid increase of the concentration of desflurane is due to stimulation of medullary centres either directly or indirectly by irritant receptors in the airway.

The most important aspect of the work reported here is that bilateral division of the vagus nerves abolished sympathoexcitation by desflurane, apart from a very small residual reflex response at each increase in concentration. It establishes the dominant role of pulmonary receptors in sympathetic stimulation by this agent, but also shows that its depressive effects at higher concentrations are centrally mediated. In contrast, both the sympathoexcitatory and other excitatory effects of nitrous oxide are thought to be centrally mediated.[19]

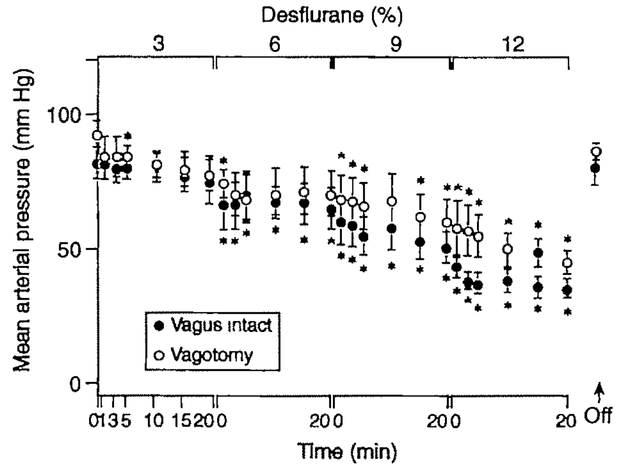

Fig 3 Summary of data of mean arterial pressure (MAP) following rapid increases in desflurane concentration in intact rabbits and following bilateral vagotomy. Off indicates values after withdrawal of desflurane. Values are expressed in mm Hg (mean (SD), $n=5$). Comparison within group with control $*P<0.05$

The responses in sympathetic activity observed here in rabbits are in keeping with previous reports of effects of relatively low concentrations of desflurane in humans. For example, Ebert and Muzi[1] observed an increase in sympathetic nerve activity, following a rapid increase in desflurane concentration from 0.5 MAC to 1.0 MAC, which was sustained when equilibrated at this concentration. A further rapid increase in its concentration from 1.0 MAC to 1.5 MAC caused a further transient increase in sympathetic activity which then decreased to a lower level, but was still greater than the value at 0.5 MAC. Although desflurane was administered at the highest concentration of 1.5 MAC for 15 min to allow equilibration of its end-tidal concentration, their recording of sympathetic activity was terminated after only ~12 min. In contrast, in the present study where overpressure was used, the equilibration of the end-tidal concentration was rapid and continuous observation of sympathetic activity was carried out for 20 min, in spite of which the results of the two studies are compatible.

Intuitively, the irritant effects of desflurane on the airway, causing coughing during the induction of anaesthesia, could be assumed to stimulate sympathetic activity, but this may not be the case. Inhalation anaesthetic agents such as desflurane may not only stimulate receptors in the airways but also could enter pulmonary interstitial tissues directly from the alveoli or indirectly via the bronchial circulation.[20] That the airways are involved was shown by Muzi and co-workers[14] in a study in humans, using double lumen tubes, where delivery of desflurane to the upper airways, including the larynx, produced increases in HR, arterial pressure and muscle sympathetic nerve activity recorded in the peroneal nerve. When the inspired desflurane concentration was rapidly increased from 5.6% to 11% in one lung and simultaneously reduced to zero in the other, there was no change in sympathetic activity. An inspired desflurane concentration of 11% administered via both lungs rather than only one, caused a greater increase in HR and arterial pressure and sympathetic activity which they related to an increase in blood concentration and a consequent action on 'extra-pulmonary receptors', and in this respect their results agree with others.[16 17] However, the possibility of a contribution to the observed increase in sympathetic activity by recruitment of additional airway and pulmonary receptors in the second lung was not considered. In addition, topical anaesthesia of the airways and relevant afferent nerves, failed to prevent sympathetic excitation during the administration of 11% desflurane and could imply that superficial airway structures are not involved.

In another study, also using double lumen tubes, in human volunteers, anaesthesia was maintained with desflurane at an end-tidal concentration of 4%.[17] When the end-tidal concentration in one lung was rapidly increased to 8% whilst simultaneously reducing it to zero in the other, the authors observed that there was an increase in HR, MAP and plasma catecholamine levels without any change in blood desflurane levels. These observations could be compatible with the findings of our study where the rise in sympathetic activity was directly correlated with desflurane concentration and hence the removal of stimulating afferent vagal activity from one lung would be more than compensated by doubling the concentration in the other one. Also, an increase in end-tidal desflurane concentration in both lungs from 4% to 8% with an increase in systemic desflurane concentration, led to the observation of an even greater increase in HR, arterial pressure and catecholamine levels.[17] The authors concluded that changes in sympathetic activity are due to stimulation of both pulmonary and 'extra-pulmonary' receptors. However, the authors did not exclude the possibility that the greater rise in HR, arterial pressure and catecholamines following the increase in desflurane concentration to 8% in both lungs could contain a contribution due to the stimulation of more airway receptors than is the case for a similar increase in one lung only. A further argument put forward by the authors supporting the idea of extra-pulmonary receptors was the observation in previous studies[3 11] that the increases in HR and MAP occurred 30 s after delivery of desflurane to the lungs compared to only 6 s following electrical stimulation of an ulnar nerve.[17] It was stated that the difference in response time observed is due to desflurane having to reach well-perfused receptors outside the airway.[17] However, Muzi and associates illustrated[14] that reflex increases in sympathetic activity and arterial pressure, assessed as an increase greater than 10% above baseline, start within 6 and 12 s, respectively, in response to the inhalation of 14.5% desflurane. Moreover, the latency to the start of reflex responses in pre-ganglionic sympathetic neurons will roughly be the same as from nociceptive stimulation of a peripheral nerve. However, the time to reach the peak effect will depend on spatial and temporal summation of both the receptors, for example for desflurane in the lungs, and the efferent sympathetic neurons. Hence there is no hard evidence for extrapulmonary receptors, which is confirmed in this study.

In a preliminary report of a study conducted on 19 subjects undergoing cardiac surgery, delivery of desflurane via the oxygenator at increasing concentrations produced an increase in plasma norepinephrine levels when it was increased from 0.75 MAC to 1.5 MAC,[16] which was not observed with isoflurane. However, desflurane could still have reached the pulmonary receptors via the bronchial and pulmonary circulation.[20] In another study in patients undergoing similar surgical procedures, the effects of desflurane on haemodynamics and plasma catecholamines were compared with sevoflurane.[18] In contrast to the previous study, where isoflurane was compared with desflurane, these authors showed that whereas the administration of desflurane to the oxygenator at 7.8% did not produce any significant change in plasma catecholamine concentrations, 2.5% sevoflurane produced a decrease. In addition, plasma catecholamines were significantly lower following the administration of sevoflurane compared with desflurane.[18]

In our study in intact rabbits, the observed increase in sympathetic activity at equilibrated desflurane end-tidal concentrations of 3% and 6% is unlikely to be baroreceptor mediated because in vagotomized animals the fall in arterial pressure was similar without sympathoexcitation. This argument is also supported by a recent study in human volunteers where a significant increase in muscle sympathetic nerve activity was observed at increasing steady-state concentrations of desflurane when the MAP was maintained constant with a phenylephrine infusion.[5]

In the vagotomized group of rabbits, there were small immediate transient increases in sympathetic activity corresponding to the rapid initial reflex responses in the intact animals. The peak increase occurred within 1 min after each change in desflurane concentration which was statistically significant for an increase of 14% above baseline at 4.5% concentration. This observation suggests that there is a small alternative afferent pathway from the lungs to the central nervous system other than via the vagus nerves, and it has been shown previously that there is a link between pulmonary inflation and systemic vascular resistance via a non-cholinergic sympathetic vasodilator pathway.[21]

In conclusion, in an intact rabbit model there were two biphasic responses in sympathetic activity to increasing concentrations of desflurane. Firstly, at each increase in concentration there was a large initial reflex response almost linearly related to the peak inspired concentration, which subsequently declined to a stable lower level during equilibration. Secondly, whereas after equilibration at lower concentrations sympathetic activity remained higher than baseline, at higher concentrations there was a major depression below baseline. The immediate sympathetic responses to rapid increases in desflurane concentrations and also that sustained at lower levels after equilibration at low concentrations, were abolished by bilateral vagotomy. There was evidence to support a small extra-vagal alternative pathway contributing to the immediate response to a sudden increase in desflurane concentration. The depression in sympathetic activity at high concentration is centrally mediated. For practical purposes, sympathoexcitation and depression caused by desflurane are mediated peripherally and centrally, respectively.

References

1 Ebert TJ, Muzi M. Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers. *Anesthesiology* 1993; **79**: 444–53

2 Pacentine GG, Muzi M, Ebert TJ. Effects of fentanyl on sympathetic activation associated with the administration of desflurane. *Anesthesiology* 1995; **82**: 823–31

3 Weiskopf B, Moore MA, Eger II EI, Noorani M, McKay L, Chortkoff B, Hart PS, Damask M. Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than rapid increase in isoflurane concentration in humans. *Anesthesiology* 1994; **80**: 1035–45

4 Moore MA, Weskopf RB, Eger II EI, Noorani M, McKay L, Damask M. Rapid 1% increases of end-tidal desflurane concentration to greater than 5% transiently increase heart rate and blood pressure in humans. *Anesthesiology* 1994; **81**: 94–8

5 Ebert TJ, Perez F, Uhrich TD, Deshur MA. Desflurane-mediated sympathetic activation occurs in humans despite preventing hypotension and baroreceptor unloading. *Anesthesiology* 1998; **88**: 1227–32

6 Muzi M, Ebert TJ. A comparison of baroreflex sensitivity during isoflurane and desflurane anesthesia in humans. *Anesthesiology* 1995; **82**: 919–25

7 Lee C, Kwan WF, Tsai SK, Chen BJ, Cheng M. A clinical assessment of desflurane anesthesia and comparison with isoflurane. *Can J Anaesth* 1993; **40**: 487–94

8 Hartman G, Kelly R, Embree P, Artusio J. Vital capacity rapid inhalation induction (VCRII) with desflurane (abstract). *Anesthesiology* 1990; **73**: A20

9 Bunting HE, Kelly MC, Milligan KR. Effect of nebulized lignocaine on airway irritation and haemodynamic changes during induction of anaesthesia with desflurane. *Br J Anaesth* 1995; **75**: 631–3

10 Zwass M, Fisher D, Welborn L, Cote CJ, Davis PJ, Dinner M, Hannallah RS, Liu LM, Sarner J, McGill WA, Alifimoff JK, Embree PB, Cook DR. Induction and maintenance characteristics of anesthesia with desflurane and nitrous oxide in infants and children. *Anesthesiology* 1992; 76: 373–8

11 Weiskopf RB, Eger II EI, Noorani M, Daniel M. Repetitive rapid increases in desflurane concentration blunt transient cardiovascular stimulation in humans. *Anesthesiology* 1994; **81**: 843–9

12 Paintal AS. Vagal sensory receptors and their reflex effects. *Physiol Rev* 1973; **53**: 159–227

13 Mills JE, Sellick H, Widdicombe JG. Activity of lung irritant receptors in pulmonary microembolism, anaphylaxis and drug-induced bronchoconstriction. *J Physiol* 1969; **203**: 337–57

14 Muzi M, Ebert TJ, Hope WG, Robinson BJ, Bell LB. Site(s) mediating sympathetic activation with desflurane. *Anesthesiology* 1996; **85**. 737–47

15 Pac-Soo CK, Ma D, Wang C, Chakrabarti MK, Whitwam JG. Specific actions of halothane, isoflurane and desflurane on sympathetic activity and Aδ and C somatosympathetic reflexes recorded in renal nerves in dogs. *Anesthesiology* 1999; **91**: 470–8

16 Ciofolo MJ, Jansson E, Johansson G, Morrison S, Reiz S. Sympathetic activation by desflurane is not mediated by airway or lung receptors. *Br J Anaesth* 1995; **74**: A128

17 Weiskopf RB, Eger II EI, Daniel M, Noorani M. Cardiovascular stimulation induced by rapid increases in desflurane concentration in humans results from activation of tracheopulmonary and systemic receptors. *Anesthesiology* 1995; **83**: 1173–8

18 Rodig G, Keyl C, Kaluza M, Kess F, Hobbhahn J. Effects of rapid increase of desflurane and sevoflurane to concentrations of 1.5 MAC on systemic vascular resistance and catecholamine response during cardiopulmonary bypass. *Anesthesiology* 1997; **87**: 801–7

19 Fukunaga AF, Epstein RM. Sympathetic excitation during nitrous oxide–halothane anaesthesia in the cat. *Anesthesiology* 1973; **39**: 23–6

20 Deffebach E, Charan B, Lakshminarayan S, Butler J. Bronchial circulation. *Am Rev Resp Dis* 1987; **135**: 463–81

21 Daly De B, Hazzledine JL, Ungar A. The reflex effects of alterations in lung volume on systemic vascular resistance in the dog *J Physiol* 1967; **188**: 331–51

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BJA

REVIEW ARTICLE

Volume replacement in the surgical patient—does the type of solution make a difference?

J. Boldt

Department of Anaesthesiology and Intensive Care, Medicine Klinikum der Stadt Ludwigshafen, Bremserstrasse 79, D-67063 Ludwigshafen, Germany

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Absolute or relative blood volume deficits often occur during surgery. The former may result from bleeding while the latter may be caused by vasodilation mediated by vasodilating substances (e.g. anaesthetics) or rewarming. Fluid deficits can also develop in the absence of obvious fluid loss secondary to generalized impairment of the endothelial barrier resulting in diffuse 'capillary leak', for example during cardiopulmonary bypass or sepsis. Hypovolaemia is associated with alterations in blood flow that are inadequate to fulfil the nutritive role of the circulation. During hypovolaemia-related haemodynamic dysfunction, the organism tries to compensate for perfusion deficits by redistribution of flow to vital organs (e.g. heart and brain), resulting in underperfusion of other organs such as the gut, kidneys, muscles and skin. Activation of the sympathetic nervous system and the renin–aldosterone–angiotensin system (RAAS) are compensatory mechanisms to maintain peripheral perfusion. Various circulating vasoactive substances and inflammatory mediators are also released. Although this compensatory neurohumoral activation is initially beneficial, it becomes deleterious in the hypovolaemic critically ill patient. Adequate restoration of intravascular volume thus remains important in managing the surgical patient.

Increased awareness of the risk of transmitting viral diseases, such as hepatitis and AIDS, has resulted in greater use of alternatives to blood in volume replacement. A reduction in haematocrit is not deleterious even in 'high-risk' patients, since compensating mechanisms are able to guarantee tissue oxygenation and systemic oxygen transport.[84 95] Nevertheless, in the critically ill surgical patient, oxygen-carrying capacity must be evaluated carefully. Although extensive information is available on the use of haemodilution, the 'safe' haematocrit is still not definitely known. In the elderly and in surgical patients with coronary artery disease, limitations of cardiac and pulmonary function will influence oxygen delivery. Nevertheless, therapy with blood or blood components should be restricted to cases presenting with severe anaemia or coagulation disorders.

There are a number of non-blood alternatives for volume replacement. The choice between colloid and crystalloid solutions continues to generate controversy,[21 51 75 95 99] and there is now an added complication in that, besides the natural colloid, albumin, several synthetic colloids have become available as plasma substitutes.[27] The 'historical' crystalloid *versus* colloid controversy focused primarily on outcome, but new concepts about critical care, the role of inflammation, immunological aspects and wound healing may change this perspective.[1 13]

Five major factors are of importance when volume replacement is being considered: the type of fluid to be administered, the amount of fluid, the criteria for guiding volume therapy, possible side-effects, and costs. It is not the aim of this review to create new guidelines for appropriate volume therapy in the surgical patient. Nor is this review to be another evidence-based analysis of the type which has raised so much discussion, as seen by the conflicting results of the study by Schierhout and Roberts[82] and the Cochrane study on albumin.[17] It is intended to be an expert-based analysis of the possible alternatives for volume replacement and of published studies on volume replacement strategies in the surgical patient.

Principles of volume replacement

Administered fluid may remain in the intravascular compartment or equilibrate with the interstitial or intracellular fluid compartments. The antidiuretic hormone system (ADH), the RAAS and the sympathetic nervous system (SNS) are involved in the control of volume and the composition of each body compartment. The principal actions of these neurohumoral systems are: to retain water in order to restore water or intravascular volume deficits; to retain sodium in order to restore intravascular volume; and to increase

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hydrostatic perfusion pressure through vasoconstriction. Enhanced activity of ADH, RAAS and SNS can occur in stress situations, for example during surgery. Although the normal response to surgery and starvation results in increased metabolic activity, a pre-existing deficit of water or intravascular volume may further increase this activity. If water or intravascular volume deficits and the stress-related stimulus of ADH, RAAS and SNS are additive, fluid management could inhibit this process through counter-regulatory mechanisms. Several attempts to inhibit or attenuate the activity of ADH and RAAS by administering different volumes of isotonic crystalloid solutions have been made.[40] [111] ADH production is known to be dependent on the maintenance of extracellular volume and, in particular, the intravascular compartment. Administration of a restricted amount of crystalloid solution could possibly replace a water deficit, but the replacement of an intravascular volume deficit would require much more volume in order to inhibit the secretory stimulus of all the hormones committed to maintain it. Thus it might be expected that the replacement of water alone would not inhibit the normal response of ADH and RAAS, whereas administration of a combination of crystalloid and colloid solutions (replacement of water deficit simultaneously with improvement in the effective intravascular volume) would achieve this goal.

The primary goal of volume administration is to guarantee stable haemodynamics by rapidly restoring circulating plasma volume. Excessive fluid accumulation, particularly in interstitial tissue, should be avoided.

Starling's hypothesis concerns the exchange of fluid across biological membranes. Colloid oncotic pressure (COP) is an important factor in determining fluid flux across the capillary membrane between the intravascular and interstitial space. Thus manipulation of COP appears to be useful for guaranteeing adequate circulating intravascular volume. The magnitude and duration of this volume effect will depend on the specific water-binding capacity of the plasma substitute and on how much of the infused solution stays in the intravascular space. Because of varying physicochemical properties, the commonly used solutions for volume replacement differ widely with regard to COP, initial volume effects and duration of stay in the intravascular compartment.

Possible strategies for volume replacement

Crystalloids

Crystalloids can be divided into hypotonic (e.g. dextrose in water), isotonic (e.g. lactated Ringer's solution) and hypertonic solutions (e.g. 7.5% saline solution). When selecting the solution for volume replacement, the electrolyte status of the patient must be known. Crystalloids freely permeate through the vascular membrane and are therefore distributed in the plasma and interstitial or intercellular fluid compartments (Table 1).[47] [111] Crystalloids are mainly distributed to the interstitial space, colloids mainly to the intravascular space.[40] After infusion of 1000 ml of saline solution, plasma volume increases by only 180 ml.[53] Only 25% of infused saline remains in the intravascular compartment, 75% being extravasated into the interstitial space.[96] Consequently, large quantities of fluid (at least four to six times the actual intravascular volume deficit) have to be infused to achieve normovolaemia when a crystalloid fluid regimen is chosen. Moreover, because of their very limited volume stabilizing effects, crystalloid infusions have to be repeated to maintain filling volume.[34] When infusing large quantities of unbuffered saline, hyperchloraemic acidosis could theoretically complicate this type of fluid therapy. Severe dilution of plasma protein concentration is accompanied by a (critical) reduction in plasma COP with the risk of increasing interstitial oedema. Thus volume replacement regimens based exclusively on infusion of the enormous amounts of crystalloids that are necessary to guarantee haemodynamic stability seem to be less adequate.[40] [47] Stein, Berand and Morisette[86] demonstrated that 70% of elderly patients suffering from circulatory shock who received crystalloids for volume stabilization developed pulmonary oedema, in contrast to 25% of a colloid-treated group. Massive crystalloid resuscitation alone is less likely to achieve adequate restoration of blood flow and tissue oxygenation.[69] In an animal (haemorrhage) experiment, Wang, Hauptman and Chaudry[106] investigated the quality of fluid resuscitation by laser Doppler flowmetry. They concluded that lactated Ringer's solution did not restore microvascular perfusion sufficiently in this situation. Others have also shown that colloids are able to restore (microcirculatory) perfusion more effectively than crystalloids.[34] In an animal model of sepsis, greater capillary luminal area, with less endothelial swelling and less parenchymal injury, was found with colloid infusion (hydroxyethyl starch (HES); pentastarch) than with Ringer's lactate.[64]

Table 1 Volume of various solutions that is necessary to expand plasma volume by 1000 ml [111] ICV, intracellular volume; IFV, interstitial fluid volume; PV, plasma volume; RL, lactated Ringer's solution

	Increase in PV (ml)	**Infused volume (ml)**	**Change in IFV (ml)**	**Increase in ICV (ml)**
5% Albumin	1000	1000		
25% Albumin	1000	250	–750	
5% Dextrose	1000	14000	+3700	9300
RL	1000	4700	+3700	

Colloids

The available colloidal solutions differ in their pharmacological characteristics and clinical effects.[76]

Albumin

This is a naturally occurring plasma protein and has long been judged to be the kind of solution from which patients would profit most ('gold standard'). Although albumin is derived from pooled human plasma, there should be no risk of disease transmission as albumin is heated and sterilized by ultrafiltration. Thus in terms of transmission of infectious disease, albumin is generally considered safe. The molecular weight of albumin is 69 kDa. Albumin 5% is iso-oncotic, whereas 20% and 25% solutions are markedly hyperoncotic, so that total plasma volume is expanded by shifting of fluid from the interstitial and intercellular to the intravascular compartment. In older studies, the oncotic force of concentrated human albumin (e.g. 20%) has been shown to reduce pulmonary oedema.[36] This effect depends on movement of albumin between the intravascular and extravascular compartments and varies greatly with the patient's pathology. In patients with altered vascular endothelial integrity (e.g. after cardiac surgery or in septic patients), albumin may pass into the interstitial space, promoting fluid shift from the intravascular compartment; interstitial volume is substantially increased[8 29 78] and tissue perfusion may be altered. Several recently published studies have questioned the value of using albumin for volume replacement[17] or for correcting hypoalbuminaemia.[33 38] Some people are born without albumin (congenital analbuminaemia), some of whom are remarkably asymptomatic.[5] The role of albumin is thus unclear.

Synthetic colloids

In contrast to albumin, which is monomeric (so all molecules are of the same size and weight), synthetic colloids are polydisperse, comprising many differently sized molecules. Large molecules only contribute minimally to the volume expansion effects, they affect viscosity and persist in the circulation. Smaller colloid molecules are quickly lost by renal filtration or diffusion into the interstitial space.

Dextrans

These are a polydisperse mixture of glucose polymers. The available preparations are 6% dextran 70 (average mol. wt 70 kDa) and 10% dextran 40 (average mol. wt 40 kDa). The increase in plasma volume after infusion of 1000 ml of dextran 70 ranges from 600 to 800 ml. The main differences between the two solutions concern their influence on the microcirculation. Infusion of dextran 40 increases microcirculatory flow because of reduced red cell and platelet sludging, volume expansion and haemodilution-induced reduction in whole blood viscosity.[3]

Gelatins

These are modified beef collagens. Gelatin was introduced in 1915 to treat shock and was used extensively during World War I. It is listed by the World Health Organization as an essential drug but in the USA it was abandoned in 1978 because of the high incidence of hypersensitivity to gelatin.[68] Three types of modified gelatin are available: cross-linked (e.g. Gelofundiol), urea-linked (e.g. Haemaccel) and succinylated (e.g. Gelofusin). These preparations contain different concentrations of electrolytes: urea-linked gelatin has a high calcium and potassium content, while succinylated preparations have low calcium and potassium content. The increase in blood volume less than the infused volume of gelatin. Because of the low molecular weight average (approximately 35 kDa), plasma half-life is only short, so repeated infusions of gelatin are necessary to maintain adequate blood volume. In spite of their limited half-life, gelatins can be used effectively in the intensive care patient.[6 26 87] In an animal experiment, the volume effects of gelatin and a starch solution were also reported to be similar.[95]

Hydroxyethylstarch (HES) preparations

These vary widely with regard to their physicochemical properties.[76] HES is a derivative of amylopectin, a highly branched starch compound. In humans and animals, amylopectin is rapidly hydrolysed by α-amylase and renally excreted. Substitution of anhydroglucose residues of the amylopectin by hydroxyethyl groups slows down metabolic degradation. The hydroxyethyl groups are introduced mainly at positions C2 and C6 of the anhydroglucose residues.

HES preparations are characterized by: concentration; the weight-averaged mean molecular weight (M_w, arithmetic mean of the molecular weight of all HES molecules); the number-averaged molecular weight (M_n), that is the median molecular weight of all HES molecules; the molar substitution (MS), that is the molar ratio of the total number of hydroxyethyl groups to the total number of glucose units; and the degree of substitution, that is the ratio of substituted glucose units to the total number of glucose molecules. They are available in a variety of concentrations (3%, 6% or 10%), molecular weights (low (LMW), 70 kDa; medium (MMW), 200–270 kDa; or high (HMW), 450 kDa) and MS (low, 0.5; moderate, 0.62; or high, 0.7). There is convincing evidence that α-amylase activity depends on the position of the hydroxyethyl groups on the glucose molecule (C2, C3, C6). The ratio of C2:C6 hydroxyethylation appears to be a key factor in the pharmacokinetic behaviour of HES and possibly also in its side-effects (e.g. accumulation). Unfortunately, the C2:C6 ratio is not yet specified by manufacturers. In the USA, only the first-generation HMW-HES *hetastarch* (concentration 6%, M_w 450 kDa, MS 0.7) is currently available for volume replacement. *Pentastarch* (concentration 10%, M_w 260 kDa, MS 0.45) is approved by the FDA only for plasmapheresis. *Pentafraction*, a diafiltered solution of hydrolysed amylopectin similar to pentastarch, has a narrower molecular weight range (M_w 280 kDa; MS 0.5) and is not commercially available.

In Europe, the range of available HES solutions is much wider, and different combinations of concentration, M_w and MS are available. The extent and duration of plasma expansion are extremely dependent on the physical and chemical characteristics of the HES solution.[76] Thus maintenance of haemodynamic stability seems to be highly dependent on the kind of HES preparation used. The different HES preparations have different effects on rheology, coagulation and oncotic pressure, and differ in their intravascular half-lives.[57 108] The type of HES solution that is most appropriate for particular patients, in terms of optimizing the macrocirculation and microcirculation, warrants further investigation.

Side-effects of volume replacement strategies

Theoretical and documented hazards are associated with each kind of volume therapy. These are discussed below.

Coagulation

One major concern with the use of synthetic colloids is a possible alteration in the coagulation system.[107] Imbalances in the normal haemostatic mechanisms are commonly seen in surgical patients, because of marked blood loss, hypothermia or activation of inflammatory pathways with subsequent activation of procoagulatory mechanisms and inhibition of anticoagulant pathways. All plasma substitutes reduce the concentration of clotting proteins by means of haemodilution.

Crystalloids are widely considered not to affect coagulation adversely although in *in vivo* and *in vitro* experiments, blood coagulation activation in moderate crystalloid haemodilution has been shown.[79] [80] Increased coagulability has been confirmed in an *in vitro* study at 30% haemodilution with saline.[28]

The natural colloid *albumin* is considered to have no significant negative effect on blood clotting. In an animal study in which dogs were resuscitated with albumin or lactated Ringer's solution, several clotting assays showed no differences, but APTT was prolonged in albumin-treated animals.[18] In an *in vitro* study using serial haemodilution (11%, 25%, 33%, 50% and 75%) and thrombelastography (TEG), Tobias and colleagues[92] found that the earliest and most profound hypocoagulable effect on the TEG was seen with albumin. Using *in vitro* bleeding time to test primary haemostasis, albumin increased the bleeding time.[24]

It is generally accepted that *dextrans* negatively influence haemostasis by reducing von Willebrand factor or by impairing platelet function.[104] This is one reason why use of dextrans has fallen markedly. When administering dextran, the concentrations of factor VIIIR:Ag and VIIIR:RCo both decrease significantly. Reduced VIIIR-RCo is associated with reduced binding to platelet membrane receptor proteins GPIb and GPIIb/IIIa, which results in decreased platelet adhesion.

Little is known of the effects of *gelatins* on perioperative haemostasis. It has been suggested that they do not significantly affect haemostatic competence.[50] In an *in vitro* study, however, significant inhibition of platelet aggregation was demonstrated by two gelatin preparations (polygelin and succinylated gelatin).[30] An *in vitro* study showed that 3.5% polygelin and 4% succinylated gelatin significantly reduced clot quality.[58] In a study of six healthy men,· infusion of 1 litre of gelatin resulted in a 1.7-fold increase in bleeding time, a substantial decrease in vWg:ag (–32%) and ristocetin cofactor (–29%) and a significant impairment of ristocetin-induced platelet aggregation.[23] These recently published data emphasize the possibility of an altered haemostatic action of gelatin independent of its haemodilution effects.

Several studies on impaired haemostasis with increased bleeding tendency after the use of *HES* have been published.[107] The majority of these studies used the first-generation HMW-HES (M_w 450 kDa, MS 0.7; hetastarch). This HES preparation may induce a type I von Willebrand-like syndrome with decreased factor VIII coagulant activity, decreased von Willebrand factor antigen and factor VIII-related ristocitin cofactor.[81] HMW-HES diminished the concentrations of VIIIR:Ag and VIIIR:RCo more markedly than LMW-HES. HMW-HES also resulted overall in the most pronounced impairment of platelet aggregation.[9] Modern MMW-HES preparations did not show the same negative effects on platelet function as HMW-HES.[9] LMW- and MMW-HES preparations with a lower MS (0.5) appear to be significantly less detrimental to coagulation[89] [93] [94] and several studies in humans have confirmed that these preparations can be used safely.[11] [93] [94] However, the results of investigations on HES in coagulation disorders are inconclusive; some experimental studies (e.g. using *in vitro* haemodilution) have demonstrated considerable alterations in haemostasis even with modern HES preparations.[28] [49]

Storage, accumulation and pruritus

Storage and accumulation of synthetic colloids in the body may occur. Gelatins and dextrans are naturally occurring substances which are fully metabolized in humans. The modified starch molecule is the basis of HES solutions–all preparations are stored and may accumulate. HES undergoes slow intravascular catabolism by α-amylase. The smaller molecules are rapidly eliminated by glomerular filtration. Depending on the HES preparation, a varying amount of the administered HES leaves the vascular department and is taken up by the reticulo-endothelial system (mononuclear phagocytic system). The process of body storage of HES is not well clarified. With regard to the mononuclear phagocytic system, storage appears to have no detrimental consequences.

Itching after administration of HES is a topic of debate. In some recently published papers, severe pruritus has been reported.[35] [61] Special features of HES-induced pruritus include long latency of onset and persistence. A dose-dependent uptake of HES was first detected in macrophages and, thereafter, in endothelial and epithelial cells. Patients suffering from pruritus consistently showed additional deposition of HES in small peripheral nerves. Most of these reports originated from patients treated for sudden deafness. These patients had received, over a long period (10–20 days), up to 2000 g (approximately 20 litre) of a HMW-HES with a high degree of substitution. The cumulative total dose of HES appears to important in this phenomenon.

The incidence of pruritus after surgery is difficult to determine, because pruritis may occur weeks or even months after administration, when the anaesthetist is no longer in contact with the patient. Occasional reports have been published. For example, 2000 ml of HES in patients undergoing urological surgery has resulted in severe pruritus.[85] However, one recently published study of more than 700 surgical patients has shown no increased incidence of pruritus after infusion of two different HES preparations (LMW- and MMW-HES) in comparison with lactated Ringer's solution.[12] Further work must be undertaken to evaluate fully the risk and mechanisms of pruritus after volume replacement, especially with HES.

Anaphylactic/anaphylactoid reactions

All colloids used for volume therapy, including the natural colloid albumin, have the potential to induce anaphylactic or anaphylactoid reactions.[32] Most commonly known in severity and frequency are dextran-induced anaphylactic reactions.[70] Even prophylaxis with monovalent hapten dextran cannot completely eliminate these reactions.[2] In a large clinical trial of approximately 20 000 patients, it was demonstrated that some gelatins produce more anaphylactic or anaphylactoid reactions than other plasma substitutes.[54] Urea-linked gelatin preparations seem to be associated with a lower incidence of inducing anaphylactic reactions than succinylated gelatin.[68] Severe (life-threatening) anaphylactic reactions may also occur with different kinds of HES preparations[20] but appear to be rare.[68]

Renal function

Impaired renal function may be another problem with the use of synthetic colloids.[25 63 105] The effects of the different volume replacement regimens on renal function are controversial. Generally, gelatins appear to have no damaging effects, although acute renal failure following infusion of gelatin has been reported.[48] Increased creatinine concentrations in patients treated with (first-generation) HMW-HES (M_w 450 kDa, MS 0.5) have been documented.[43] In a retrospective analysis of patients undergoing kidney transplantation in whom HES with a high degree of substitution (0.62) was infused, 'osmotic-nephrosis-like lesions' were seen on kidney biopsies.[55] These lesions, however, had no negative influence on graft function or serum creatinine concentration 3 and 6 months after transplantation. Cittanova and colleagues[15] demonstrated that the use of 6% HES (M_w 200 kDa, MS 0.62) (2100±660 ml) in brain-dead donors resulted in impaired renal function in kidney transplant recipients (higher serum creatinine concentrations and a more frequent incidence of haemodialysis compared with a gelatin-treated group). Thus, HES preparations with high M_w or a high degree of substitution, or both, may have detrimental effects on renal function. It is not known whether HES preparations with a lower M_w or a lower degree of substitution also impair renal function. The most likely mechanism of causing renal dysfunction is the induction of hyperviscosity of the urine by (repeated) infusion of hyperoncotic colloids in dehydrated patients.[3]

Glomerular filtration of hyperoncotic molecules from colloids causes a hyperviscous urine and stasis, resulting in obstruction of the tubular lumen. There is no convincing evidence that colloids induce renal problems in normally hydrated surgical patients.[3]

Monitoring of volume replacement therapy

Assessing and guiding adequate volume therapy remains a challenge. The aim of appropriate monitoring is to avoid insufficient fluid infusion or fluid overload ('fluid failure'). Standard haemodynamic data, such as arterial pressure and heart rate, are often unreliable in detecting volume deficits or guiding volume therapy accurately. In spite of some negative data,[19] pulmonary artery catheters are still widely used. However, cardiac filling pressures (central venous pressure (CVP) and pulmonary capillary wedge pressure) are often misleading for assessing optimal left ventricular loading. Cardiac filling pressures may be influenced by several factors other than blood volume, including those affecting cardiac performance, vascular compliance and intrathoracic pressure. Particularly in patients with altered ventricular compliance, commonly monitored parameters such as CVP, right atrial pressure or right ventricular pressure are not always sufficient to judge loading conditions. Echocardiography appears to be the most specific monitoring instrument, but because of its expense it is not available for every surgical patient during and after operations. Guided by oesophageal Doppler ultrasonography, Sinclair, James and Singer[83] assessed whether intraoperative intravascular volume optimization improved outcome and shortened hospital stay after repair of proximal femoral fracture. The patients in the control group received intraoperative crystalloids (mean 1000 ml, range 700–1250 ml) while those in the protocol group received crystalloids (mean 725 ml, range 500–1000 ml) plus HES (mean 750 ml, range 550–950 ml) to maintain maximal stroke volume. Hospital stay was significantly shorter for patients in the protocol group (mean approximately 11 days) than for those in the control group (20 days).

Perturbations of organ perfusion are thought to be of fundamental importance in the pathogenesis of organ dysfunction.[73] The importance of occult hypovolaemia in the development of organ perfusion deficits has been supported by several studies.[31 66] There is no reliable, optimal method for routine clinical detection of perfusion deficits. Haemodynamic parameters such as cardiac index, $\dot{V}_{O_2}$ and $\dot{D}_{O_2}$ are not optimal measures of the adequacy of regional or microcircular perfusion.[39] The hypovolaemic patient is at risk of splanchnic hypoperfusion with subsequent development of bacterial translocation and systemic inflammatory response syndrome (SIRS).[67 90] Abnormalities of splanchnic perfusion may coexist with normal systemic haemodynamic and metabolic parameters.[59] Measurement of gastric intramucosal pH (pH_i) can help diagnose and monitor (hypovolaemia-related) splanchnic hypoperfusion and appears to be more useful for predicting postoperative complications.[66]

Table 2 Volume replacement in adult surgical patients COP: colloid oncotic pressure, CRP, C-reactive protein, CVP, central venous pressure; HES, hydroxyethyl starch solution; HR, heart rate; MAP, mean arterial pressure, PCWP, pulmonary capillary wedge pressure, PPS, plasma protein solution, PRBC, packed red blood cells; RL, lactated Ringer's solution

Reference	Substances compared	Surgery	Aim	Conclusion
Halonen, Linko and Myllyla (1987)[41]	6% HES 120/0.6 (n=5), 6% dextran 70 (n=5) and 4% albumin/blood (n=5)	major abdominal surgery	fixed doses	no difference in bleeding/coagulation, outcome not shown
Hedstrand and colleagues (1987)[45]	PPS (n=142) and 6% dextran (n=133)	'major' surgery	to replace blood loss	similar postoperative complications; outcome not shown
Gold and colleagues (1990)[37]	5% albumin (n=20) and 6% HES 450/0.7 (n=20)	abdominal aortic surgery	HES 2 g kg^{-1} albumin 1 g kg^{-1}	no differences in haemostasis or bleeding; outcome not shown
Prien and colleagues (1990)[74]	10% HES 200/0.5 (n=6), 20% albumin (n=6) and RL (n=6)	major abdominal surgery	maintain CVP level	no differences in coagulation, RL led to highest intestinal oedema; outcome not shown
von Sommoggy and colleagues (1990)[103]	6% HES 450/0.7 (n=11) and 5% albumin (n=13)	major vessel surgery	MAP, HR CVP, PCWP, blood loss	no differences in haemodynamics or coagulation; outcome not shown
Pertilla, Salo and Peltola (1990)[72]	gelatin (n=9), crystalloids (n=9) and 6% dextran (n=8)	abdominal surgery	fixed doses (500 ml)	no differences in fibronectin, CRP or total protein, outcome not shown
Penner, Fingerhut and Tacke (1990)[71]	10% HES 270/0.5 (n=20) and 3.5% PPS (n=20)	total hip replacement	fixed doses (1000 ml)	no differences in haemodynamics, coagulation or bleeding; outcome not shown
Hankeln, Senker and Beez (1990)[42]	10% HES 200/0.5 (n=20) and 5% albumin (n=20)	abdominal aortic surgery	PCWP > 10 mm Hg (up to 18 mm Hg)	HES gave greater improvement in haemodynamics and oxygen transport; outcome not shown
Dawidson and colleagues (1991)[22]	RL (n=10) and 3% dextran 60 + RL (n=10)	aortic reconstructive surgery	PCWP>10 mm Hg urine >30 ml h^{-1}	body weight increased with RL, PV maintained with dextran; outcome not shown
Claes and colleagues (1992)[16]	6% HES 450/0.7 (n=10), (n=9) 5% albumin (n=10); (n=11)	brain surgery and hysterectomy	fixed doses 1000 ml	no differences in haemostasis or blood loss, outcome not shown
Rosencher and colleagues (1992)[77]	4% albumin (n=30) and 6% HES 200/0.62 (n=30)	total hip replacement	compensate for blood loss	no differences in bleeding or haemostasis, outcome not shown
Vogt, Bothner and Georgieff (1994)[100]	5% albumin (n=20) and 6% HES 200/0.5 (n=20)	vessel, orthopaedic surgery	1000, 2000 or 3000 ml	no change in haemodynamics, haemostasis, bleeding or COP, outcome not shown
McFarlane and Lee (1994)[60]	0.9% saline (n=15) and Plasmalyte 148 (n=15)	major abdominal surgery	fixed dose 'clinical state'	effect on haemodynamics not shown, saline led to increased Cl$^-$ and base excess, outcome not shown
Thurner (1994)[91]	10% HES 200/0.5 (n=30), 6% HES 40/0.5 (n=30), 3.5% gelatin (n=30) and 6% dextran 60 (n=30)	general, abdominal surgery	maintain 'haemodynamics'	more gelatin necessary, gelatin was associated with reduced stability and lower platelet aggregation; outcome not shown
Hippala and colleagues (1995)[46]	4% HES 120/0.7 (n=15), 3% dextran 70 (n=15), 5% albumin (n=15) and 6% HES 120/0.7 (n=15)	abdominal urological surgery	replace blood loss	no differences in effect on COP or diuresis; similar clinical effects; outcome not shown
Lisander and colleagues (1996)[56]	4% albumin (n=20) and 6% dextran 70 (n=20)	hip arthroplasty	maintain normovolaemia	dextran led to higher blood loss, and greater PRBC requirement; outcome not shown
Vogt and colleagues (1996)[101]	6% HES 200/0.5 (n=20) and 5% albumin (n=21)	hip arthroplasty	replace blood loss	no differences in haemodynamics, haemostasis, blood loss or renal function; no difference in outcome
Marik, Iglesias and Marini (1997)[59]	6% HES 450/0.7 (n=15) and crystalloids (n=15)	repair of aortic aneurysm	PCWP 10–14 mm Hg	no differences in haemodynamics, blood loss or transfusions, splanchnic perfusion improved with HES; no difference in outcome
Beyer and colleagues (1997)[7]	3% modified gelatin (n=22) and 6% HES (n=19)	hip surgery	haemodynamics 'clinical criteria'	no differences in haemodynamics, haemostasis or renal function; outcome not shown
Bothner, Georgieff and Vogt (1998)[12]	6% HES 200/0.5 (n=247), 6% HES 200/0.5 (n=240) and RL (n=241)	minor surgery	fixed dose 500 ml HES or 1000 ml RL	no difference in itching (questionnaire); outcome not shown
Vogt and colleagues (1998)[102]	6% HES 200/0.5 (n=20) 5% albumin (n=20)	major urological surgery	according to blood loss	no differences in haemodynamics or blood loss, outcome not shown

Table 3 Volume replacement in paediatric surgical patients BP, blood pressure, COP, colloid oncotic pressure, HR, heart rate

Reference	Substances compared	Surgery	Aim	Conclusion
Hausdorfer. Hagemann and Heine (1986)[44]	5% albumin ($n=15$) and 6% HES 40/0.5 ($n=15$)	3 h of surgery (type of surgery not specified)	compensate for blood loss, keep HR and BP stable	no differences in renal function or haemostasis, HES recommended, outcome not shown
Stoddardt, Rich and Sury (1996)[88]	gelatin ($n=15$) and 4 5% albumin ($n=15$)	major abdominal surgery	maintain normovolaemia	no difference in COP, albumin recommended, outcome not shown

Table 4 Approximate volume effects of different colloidal plasma substitutes HES; hydroxyethylstarch solution

Colloid	Volume-restoring effect (h)	Initial effect (%)
Long-acting	5–6	
6% Dextran 60		120
6% HES 450/0 7		100
6% HES 200/0.62		100
Medium-acting	3–4	
10% Dextran 40		200
6% HES 200/0.5		100
10% HES 200/0 5		130
Short-acting	1–2	
6% HES 70/0 5		70
3% Gelatin		70
5% Albumin		70–90

Literature analysis of volume replacement studies in surgery

Published studies dealing with volume or fluid therapy in surgery were identified using Medline; articles written in English, German and French were analysed. Experimental or animal studies were excluded because animal models cannot completely mimic the changes found in humans. Studies in septic intensive care patients and patients suffering from ARDS were not included. No studies on volume replacement in cardiac surgery were analysed and prehospital fluid therapy and volume replacement in trauma patients were also excluded. Only studies comparing different solutions for volume therapy in the perioperative period were analysed. Studies using preoperative acute normovolaemic haemodilution as a blood conservation technique and comparing different solutions for replacement of the withdrawn blood were excluded. Studies that focused exclusively on postoperative volume replacement in intensive care were not reviewed. Unlike recently published reviews on this topic,[17 82] only studies published in the period from 1985 to 1998 were included, as several innovative strategies have been developed in the last 15 years including improved surgical and anaesthetic techniques, monitoring, ventilation strategies and postoperative critical care management.

In the 21 studies on adults reviewed here (Table 2), patients undergoing major vessel surgery (e.g. abdominal aortic surgery), major abdominal surgery (e.g. pancreatic duodenectomy) or orthopaedic surgery (hip surgery) were most often studied.[7 12 16 22 37 41 42 45 46 56 59 60 71 72 74 77 91 100–103] Only one controlled randomized study on patients undergoing neurosurgery was found.[16] The populations studied by different authors varied widely, with from five to 247 patients in each volume group. The majority of these studies compared different colloids for volume replacement (e.g. albumin versus HES). This is surprising as some guidelines for volume therapy recommended crystalloids as first choice in the surgical patient.[98] The American College of Surgeons classify blood loss by acute haemorrhage into four groups, ranging from up to 750 ml to >2000 ml, and specify some additional variables (such as blood pressure and urine output).[62] Fluid replacement should be performed with crystalloids (3:1 rule). It is not clear from which studies this recommendation was derived. One interesting study compared the effects of crystalloids (lactated Ringer's solution) with colloid volume replacement (albumin and 6% HES (M_w 200 kDa, MS 0.5)).[74] A significantly greater degree of intestinal oedema occurred with Ringer's lactate. This is of particular importance as patients undergoing major abdominal surgery were studied, and considerable intestinal oedema is disadvantageous in such patients. The negative effects of crystalloid volume replacement on the gut, in comparison with colloids, have been noted.[59]

Dawidson and colleagues showed that crystalloids had a limited effect on plasma volume.[22] The infused volume in the viewed studies ranged from 500 to 3000 ml Either fixed doses of the different solutions were administered or the amount of fluid infusion was adjusted with regard to haemodynamic variables (e.g. mean arterial pressure, heart rate or CVP). Some studies adjusted volume therapy only according to 'clinical estimation', to 'maintain haemodynamics' or 'according to blood loss'.

Several studies were carried out to evaluate possible alteration of haemostasis by synthetic colloids. The majority of studies compared different HES preparations with albumin. Use of dextran led to more bleeding and use of more packed red blood cells than use of albumin.[56] Use of HES was not associated with differences in haemostatic competence or increased bleeding tendency in comparison with albumin. Haemodynamic efficacy has also been investigated. All such studies showed similar results, namely that there were no differences in haemodynamic efficacy of albumin *versus* synthetic colloids (e.g. HES).

Some studies concerned the possible negative side-effects of synthetic colloids (e.g. on kidney function or itching). Renal function was not impaired by HES[7 46 101] and one study of more than 700 patients demonstrated no difference in the incidence of itching between HES-based and Ringer's lactate-based volume therapy in patients undergoing minor surgery.[12]

There has been much debate about which endpoints should be used to assess the benefits of volume replacement regimen–patient outcome, length of stay on the ICU or physician's satisfaction? Does a certain strategy of volume replacement improve patient survival or does it just delay death for a limited period of time?[110] Outcome was not given in most of the analysed studies, so the influence of different volume replacement strategies on it cannot be determined.

Only two studies were found comparing different volume replacement regimen in children (Table 3).[44 88] In children undergoing abdominal surgery, gelatin and HES were compared with albumin. Neither study found a difference in organ function or haemostasis and both studies came to a similar conclusion, namely that synthetic colloids appear to be safe for volume replacement in children and can widely replace albumin for volume therapy in this situation.

Conclusions

Well-balanced volume therapy is essential in managing patients undergoing surgery. Allogenic blood and blood products will still have a place in managing these patients. The 'ideal' plasma substitute for volume replacement remains a matter of dispute, but its requirements can be defined. Advantages and disadvantages of colloids *versus* crystalloids for volume replacement have been discussed. Recently published meta-analyses or evidence-based medicine analyses[10 14 82 97] appear to be unhelpful in solving this problem. With their conflicting results more questions arise than answers are given (see also the *BMJ* website at http://www.bmj.com).

Perioperative fluid requirements will depend on the length and complexity of surgery. The primary goal for volume replacement therapy is to augment intravascular volume and to maintain stable haemodynamics. Microcirculatory organ perfusion should also be guaranteed. The benefits and disadvantages of each solution for volume replacement have to be considered, including the effects on haemostasis, renal function and other organ systems. The choice of solution for maintenance of circulating volume in the individual patient should be based on its pharmacokinetics and pharmacodynamics as well as on the patients' pathophysiology (Table 4). In spite of the absence of any convincing evidence, consensus guidelines have been published recommending crystalloids as first choice for volume replacement.[98] Crystalloids appear to be less appropriate for resuscitation of the intravascular space because they are mainly distributed to the interstial space. Colloids are more appropriate for treating intravascular volume deficits. Human albumin is still widely used for volume replacement in the absence of convincing data in the literature.[10] Synthetic colloids are effective alternative plasma substitutes. The different preparations appear to vary little with regard to their (acute) haemodynamic efficacy, but they show varying (negative) effects on coagulation and varying risk of inducing severe, life-threatening anaphylactic reactions. The physicochemical properties of the various synthetic colloids have mostly been neglected in the different meta-analyses. Because of variability between individual colloids, it is not appropriate to combine studies using different colloids. The lower costs of these solutions is a powerful argument for using synthetic colloids rather than albumin. It has been calculated that a change to the cheapest fully-approved colloid on the USA market may save US $300 million annually.[65] There are no convincing guidelines regarding the choice of fluid for volume replacement in the surgical patient. This review is not an attempt to create a 'cook book' for volume replacement but, rather, summarizes the results of important studies on this problem. It has to be doubted whether there will be a definite solution. Conflicting results from different studies probably result from variations in clinical protocols, selection of patients, and criteria for blood or volume administration. A randomized control trial comparing two different solutions would require over 6500 (comparable) patients to detect an excess mortality of 4%.[109] Which fluid is more effective is unlikely to be answered adequately in terms of mortality. It has been questioned whether meta-analyses are helpful for examining the effects of crystalloid or colloid fluid resuscitation in this respect,[4] because mortality was never an endpoint of any of the crystalloid or colloid studies. Organ function, endothelial inflammation, perfusion and other physiological variables should be taken into account when comparing the effects of different fluids. Future studies must focus on how those patients are identified who may benefit from a particular kind of volume replacement strategy and on the improvement of monitoring measures to recognize volume deficits and to guide volume therapy. In spite of many years of intensive research on this problem we remember Cecil Rhodes' remark, 'So little done–so much to do.'

References

1 Alexander JW. Mechanism of immunologic suppression in burn injury. *J Trauma* 1990; **30** (Suppl): S70–5

2 Allhoff T, Lenhart FP. Severe dextran-induced anaphylactic/anaphylactoid reaction inspite of hapten prophylaxis. *Infusionsther Transfusionsmed* 1993; **20**: 301–6

3 Arfors KE, Buckley P. Pharmacological characteristics of artificial colloids. *Bailliere's Clin Anaesthesiol* 1997; **11**: 15–47

4 Astiz ME, Rackow EC. Crystalloid–colloid controversy revisited. *Crit Care Med* 1999; **27**: 34–5

5 Baldo-Enzi G, Baiocchi MR, Vigna G, Andrian C, Mosconi C, Fellin R. Analbuminemia: a natural model of metabolic compensatory systems. *J Inher Metab Dis* 1987; **10**: 317–29

6 Beards SC, Watt T, Edwards JD, Nightingale P, Farragher EB. Comparison of the hemodynamic and oxygen transport responses to modified fluid gelatin and hetastarch in critically ill patients: a prospective, randomized trial. *Crit Care Med* 1994; **22**. 600–5

7 Beyer R. Harmening U, Rittmeyer O, Zielmann S, Mielck F, Kazmaier S, Kettler D. Use of modified gelatin and hydroxyethyl

starch for volume replacement in major orthopaedic surgery. *Br J Anaesth* 1997; **78**: 44–50

8 Boldt J, von Bormann B, Kling D, Borner U, Mulch J, Hempelmann G. Colloidosmotic pressure and extravascular lung water after extracorporeal circulation. *Herz* 1985; **10**: 366–75

9 Boldt J, Knothe C, Zickmann B, Andres P, Dapper F, Hempelmann G. Influence of different intravascular volume therapy on platelet function in patients undergoing cardiopulmonary bypass. *Anesth Analg* 1993; **76**: 1185–90

10 Boldt J, Lenz M, Kumle B, Papsdorf M. Volume replacement strategies on intensive care units: results from a postal survey. *Intensive Care Med* 1998; **24**: 147–51

11 Boldt J, Muller M, Mentges D, Papsdorf M, Hempelmann G. Volume therapy in the critically ill: is there a difference? *Intensive Care Med* 1998; **24**. 28–36

12 Bothner U, Georgieff M, Vogt NH. Assessment of the safety and tolerance of 6% hydroxyethyl starch (200/0.5) solution: a randomized, controlled epidemiology study. *Anesth Analg* 1998; **86**: 850–6

13 Chaudry IH, Ayala A. Immune consequences of hypovolemic shock and resuscitation. *Curr Opin Anesth* 1993; **6**· 385–92

14 Choi P, Yip G, Quinonez L, Cook D. Crystalloids versus colloids in fluid resuscitation: a systematic review. *Crit Care Med* 1999, **27**: 200–10

15 Cittanova ML, Leblanc I, Legendre C, Mouquet C, Riou B, Coriat P. Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. *Lancet* 1996; **348**: 1620–22.

16 Claes Y, van Hemelrijk J, van Gerven M, Arnout J, Vermylen J, Weidler B, van Aken H. Influence of hydroxyethyl starch on coagulation in patients during the perioperative period. *Anesth Analg* 1992; **75**· 24–30

17 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998; **317**: 235–9

18 Cogbill TH, Moore EE, Dunn EL, Cohen RG. Coagulation changes after albumin resuscitation. *Crit Care Med* 1981; **9**· 22–6

19 Connors AF Jr, Speroff T, Dawson NV *et al.* The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA* 1996; **276**: 889–97

20 Cullen MJ, Singer M. Severe anaphylactoid reaction to hydroxyethyl starch. *Anaesthesia* 1990; **45**: 1041–2

21 Dawidson I. Fluid resuscitation of shock: current controversies. *Crit Care Med* 1989; **17**. 1078–80

22 Dawidson IJ, Willms CD, Sandor ZF, Coorpender LL, Reisch JS, Fry WJ. Ringer's lactate with or without 3% dextran-60 as volume expanders during abdominal aortic surgery. *Crit Care Med* 1991; **19**: 36–42

23 de Jonge E, Levi M, Berends F, van der Emde AE, ten Cate JW, Stoutenbeek CP. Impaired haemostasis by intravenous administration of a gelatin-based plasma expander in human subjects. *Thromb Haemost* 1998; **79**· 286–90

24 Dietrich G, Orth D, Haupt W, Kretschmer V. Primary hemostasis in hemodilution–infusion solutions. *Infusionstherapie* 1990; **17**: 214–16

25 Druml W, Polzleitner D, Laggner AN, Lenz K, Ulrich W. Dextran-40, acute renal failure, and elevated plasma oncotic pressure. *New Engl J Med* 1988; **318**: 252–3

26 Edwards JD, Nightingale P, Wilkins RG, Faragher EB. Hemodynamic and oxygen transport response to modified fluid gelatin in the critically ill patients. *Crit Care Med* 1988; **17**: 996–8

27 Edwards JD. A new debate: colloid versus colloid? In: Vincent JL, ed. *Yearbook of Intensive Care and Emergency Medicine*. Berlin: Springer, 1994; 152–64

28 Egli GA, Zollinger A, Seifert B, Popvic D, Pasch T, Spahn DR. Effects of progressive haemodilution with hydroxyethyl starch, gelatin and albumin on blood coagulation. *Br J Anaesth* 1997; **78**: 684–9

29 Ernest D, Belzberg AS, Dodeck PM. Distribution of normal saline and 5% albumin infusions in septic patients. *Crit Care Med* 1999; **27**: 46–50

30 Evans PA, Glenn JR, Heptinstall S, Madira W. Effects of gelatin-based resuscitation fluids on platelet aggregation. *Br J Anaesth* 1998; **81**: 198–202

31 Fiddian-Green RG. Gut mucosal ischaemia during cardiac surgery. In: Taylor K, ed. *Seminars in Cardiovascular Surgery*. Philadelphia· W. B. Saunders, 1990; 1–11

32 Fisher MM, Brady PW. Adverse reactions to plasma volume expanders. *Drug Safety* 1990; **15**: 86–93

33 Foley EF, Borlase BC, Dzik WH, Bistrian BR, Benotti PN. Albumin supplementation in the critically ill. *Arch Surg* 1990; **125**: 739–42

34 Funk W, Baldinger V. Microcirculatory perfusion during volume therapy. *Anesthesiology* 1995, **82**: 975–82

35 Gall H, Schultz KD, Boehncke WH, Kaufmann R. Clinical and pathophysiological aspects of hydroxyethyl starch-induced pruritus: evaluation of 96 cases. *Dermatology* 1996, **192**: 222–6

36 Giordano JM, Campbell DA, Joseph WL. The effect of intravenously administered albumin on dogs with pulmonary interstitial edema. *Surg Gynecol Obstetr* 1973; **137**. 593–9

37 Gold MS, Russo J, Tissot M, Weinhouse G, Riles T. Comparison of hetastarch to albumin for perioperative bleeding in patients undergoing abdominal aortic aneurysm surgery. *Ann Surg* 1990; **125** 482–5

38 Golub R, Sorrento JJ, Cantu R, Nierman DM, Moideen A, Stein D. Efficacy of albumin supplementation in the surgical intensive care unit: A prospective, randomized study. *Crit Care Med* 1994; **22**: 613–9

39 Gutierrez G, Bismar H, Dantzker DR, Silva N. Comparison of gastric intramucosal pH with measures of oxygen transport and consumption in critically ill patients. *Crit Care Med* 1992; **20**: 451–7

40 Haljamae H. Volume substitution in shock. *Acta Anaesthesiol Scand* 1993; **37** (Suppl): S25–8

41 Halonen P, Linko K, Myllyla G. A study of haemostasis following use of high doses of hydroxyethyl starch 120 and dextran in major laparotomies. *Acta Anaesthesiol Scand* 1987; **31**. 320–4

42 Hankeln K, Senker R, Beez M. Comparative study of the intraoperative effectiveness of 5% human albumin or 10% hydroxyethyl starch (HAES-steril) in terms of hemodynamics and oxygen transport in 40 patients. *Infusionsther* 1990; **17**· 135–40

43 Haskell PL, Tannenberg AM. Elevated urinary specific gravity in acute oligure renal failure due to hetastarch administration. *NY State J Med* 1988; **88**: 387–8

44 Hausdorfer J, Hagemann H, Heine J. Comparison of plasma substitutes human albumin 5% and hydroxyethyl starch 6% in paediatric anaesthesia. *Anaesth Intensivther Notfallmed* 1986; **21**: 137–42

45 Hedstrand U, Hogman C, Zaren B, Lundkvist B. Postoperative complications after blood replacement with or without plasma. A trial in elective surgery. *Acta Chir Scand* 1987, **153**: 501–5

46 Hiippala S, Linko K, Myllylä G, Lalla M, Hekali R, Makelainen A. Replacement of major surgical blood loss by hypo-oncotic or conventional plasma substitutes. *Acta Anaesthesiol Scand* 1995; **39**: 228–35

47 Hillman K, Bishop G, Bristow P. The crystalloid versus colloid controversy: present status. *Bailliere's Clin Anaesthesiol* 1997; **11**: 1–13

48 Hussain SF, Drew PJT. Acute renal failure after infusion of gelatins. *BMJ* 1989; **299**: 1137–8.

49 Jamnicki M, Zollinger A, Seifert B, Popovic D, Pasch T, Spahn DR. The effect of potato starch derived and corn starch derived hydroxyethyl starch on *in vitro* blood coagulation. *Anaesthesia* 1998; **53**: 638–44

50 Karoutsos S, Nathan N, Lahrimi A, Grouille D, Feiss P, Cox DJA. Thrombelastogram reveals hypercoagulability after administration of gelatin solution. *Br J Anaesth* 1999; **82**: 175–7

51 Kreimeier U, Peter K. Strategies of volume therapy in sepsis and systemic inflammatory response syndrome. *Kidney Int* 1998; **53** (Suppl 64): S75–9

52 Shatney CH, Chaudry IH. Hydroxethylstarch administration does not depress reticuloendothelial function or increase mortality from sepsis. *Circ Shock* 1984; **13**: 21–6

53 Lamke LO, Liljedahl SO. Plasma volume changes after infusion of various plasma expanders. *Resuscitation* 1976; **5**: 93–8

54 Laxenaire M, Charpentier C, Feldman L. Reactions anaphylactoides aux substitutes colloidaux du plasma: incidence, facteurs de risque, mecanismes. *Ann Fr Anest Reanimat* 1994, **13**: 301–10

55 Legendre C, Thervet E, Page B, Percheron A, Noel LH, Kreis H. Hydroxyethylstarch and osmotic-nephrosis-like lesions in kidney transplantation. *Lancet* 1993; **342**: 248–9

56 Lisander B, Jacobsson SA, Ivarsson I, Vegfors M, Engdahl O. Giving both enoxaparin and dextran increases the need for transfusion in revison hip arthroplasty. *Eur J Surg* 1996; **162**: 861–6

57 London MJ, Ho SJ, Triedman JK, Verrier ED, Levin J, Merrick SH *et al.* A randomized clinical trial of 10% pentastarch (low molecular weight hydroxyethyl starch) versus 5% albumin for plasma volume expansion after cardiac operations. *J Thorac Cardiovasc Surg* 1989; **97**: 785–97

58 Mardel SN, Saunders FM, Allen H, Menezes G, Edwards CM, Ollerenshaw L *et al.* Reduced quality of clot formation with gelatin-based plasma substitutes. *Br J Anaesth* 1998; **80**: 204–7

59 Marik PE, Iglesias J, Marini B. Gastric intramucosal pH changes after volume replacement with hydroxyethyl starch or crystalloid in patients undergoing elective abdominal aortic aneurysm repair. *J Crit Care* 1997; **12**: 51–5

60 McFarlane C, Lee A. A comparison of Plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. *Anaesthesia* 1994; **49**: 779–81

61 Metze D, Reimann S, Szepfalusi Z, Bohle B, Kraft D, Luger TA. Persistent pruritus after hydroxyethyl starch infusion therapy: a result of long-term storage in cutaneous nerves. *Br J Dermatol* 1997; **136**: 553–9

62 Miller RD. Update on blood transfusions and blood substitutes. *Anesth Analg* 1999; **88** (IARS Suppl): S71–8

63 Moran M, Kapsner C. Acute renal failure associated with elevated plasma oncotic pressure. *New Engl J Med* 1987; **317**: 150–3

64 Morisaki H, Sibbald WJ. Issues in colloid and transfusion therapy of sepsis. In: Vincent, ed *Yearbook of Intensive Care and Emergency Medicine*. Berlin: Springer, 1993; 357–72

65 Munoz E. Costs of alternative colloid solutions. *Infect Surg* 1987; **11**: 643–8

66 Mythen MG, Webb AR. The role of gut mucosal hypoperfusion in the pathogenesis of postoperative organ dysfunction. *Intensive Care Med* 1994; **20**: 203–9

67 Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Ann Surg* 1995; **130**: 423–9

68 Nearman HS, Herman ML. Toxic effects of colloids in the intensive care unit. *Crit Care Clin* 1991; **7**: 713–23

69 Neumann M, Demling RH. Colloid vs crystalloid: a current perspective. *Intensive Crit Care Digest* 1990; **9**: 3–5

70 Paull J. A prospective study of dextran-induced anaphylactoid reactions in 5745 patients. *Anaesth Intensive Care* 1987; **15**: 165–7

71 Penner M, Fingerhut D, Tacke A. Effect of a new 10% hydroxyethyl starch solution HES 270/0.5 on blood coagulation, blood loss and hemodynamics in comparison with 3.5% PPL. *Infusionstherapie* 1990; **17**: 314–18

72 Pertilla J, Salo M, Peltola O. Effects of different plasma substitutes on plasma fibronectin concentrations in patients underging abdominal surgery. *Acta Anaesthesiol Scand* 1990; **34**: 304–7

73 Pittard AJ, Hawkins WJ, Webster NR. The role of the microcirculation in the multi-organ dysfunction syndrome. *Clin Intensive Care* 1994; **5**: 186–90

74 Prien T, Backhaus N, Pelster F, Pircher W, Bünte H, Lawin P. Effect of intraoperative fluid administration and colloid osmotic pressure on the formation of intestinal edema during gastrointestinal surgery. *J Clin Anaesth* 1990; **2**: 317–23

75 Prough DS, Johnston WE. Fluid restoration in septic shock: no solution yet. *Anesth Analg* 1989; **69**: 699–704

76 Quon CF. Clinical pharmacokinetics and pharmacodynamics of colloidal plasma volume expanders. *J Cardiothorac Anesth* 1988; **2** (Suppl 1): S13–23

77 Rosencher N, Vassilieff N, Guigonis V, Toulin P, Conseiller C. Comparison of effects of Elohes and albumin on hemostasis in orthopedic surgery. *Ann Fr Anesth Reanim* 1992; **11**: 526–30

78 Royston D, Minty B, Higgenbottom TW. The effect of surgery with cardiopulmonary bypass on alveolar–capillary barrier function in human beings. *Ann Thorac Surg* 1985; **40**: 139–44

79 Ruttmann TG, James MFM, Viljoen JF. Haemodilution induces a hypercoagulable state. *Br J Anaesth* 1996; **76**: 412–14

80 Ruttmann TG, James MFM, Aronson I. *In vivo* investigation into the effects of haemodilution with hydroxyethyl starch (200/0.5) and normal saline on coagulation. *Br J Anaesth* 1998; **80**: 612–6

81 Sanfelippo MJ, Suberviola PD, Geimer NF. Development of a von Willebrand-like syndrome after prolonged use of hydroxyethyl starch. *Am J Clin Pharmacol* 1987; **88**: 653–5

82 Schierhout G, Roberts I. Fluid resuscitation with colloids or crystalloids in critically ill patients: a systematic review of randomised trials. *BMJ* 1998; **316**: 961–4

83 Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *BMJ* 1997; **315**: 909–12

84 Spahn DR, Leone BJ, Reves JG, Pasch T. Cardiovascular and coronary physiology of acute isovolemic hemodilution: a review of nonoxygen-carrying and oxygen-carrying solutions. *Anesth Analg* 1994; **78**: 1000–21

85 Spittal MJ, Findlay GP. The seven year itch. *Anaesthesia* 1995; **50**: 913–14

86 Stein L, Berand J, Morisette M. Pulmonary edema during volume infusion. *Circulation* 1975; **52**: 483–9

87 Stockwell MA, Scott A, Day A, Riley B, Soni N. Colloid solutions in the critically ill. *Anaesthesia* 1992; **47**: 7–9

88 Stoddart PA, Rich P, Sury MRJ. A comparison of 4.5% albumin and haemaccel in neonates undergoing major surgery. *Paediatr Anaesth* 1996; **6**: 103–6

89 Strauss RG. Review of the effects of hydroxyethyl starch on the blood coagulation system. *Transfusion* 1981; **21**: 299–309

90 Takala J. Splanchnic perfusion in shock. *Intensive Care Med* 1994, **20**: 403–4

91 Thurner F. Effects of four diffferent plasma expanders on plasmatic coagulation and platelet function. *Intensiv Notfallbehandlung* 1994; **19**: 8–13

92 Tobias MD, Wambold D, Pilla MA, Greer F. Differential effects of serial hemodilution with hydroxyethyl starch, albumin, and 0.9% saline on whole blood coagulation. *J Clin Anesth* 1998; **10**: 366–71

93 Treib J, Haass A, Pindur G, Grauer MT, Wenzel E, Schimrigk. All medium starches are not the same: influence of hydroxyethyl substitution of hydroxyethyl starch on plasma volume, hemorrheologic conditions, and coagulation. *Transfusion* 1996; **36**: 450–5

94 Treib J, Haass A, Pindur G. Coagulation disorders caused by hydroxyethyl starch. *Thromb Haemost* 1997; **78**: 974–83

95 van der Linden P, Schmartz D, DeGroote F, Mathieu N, Willaert P, Rausin I, Vincent JL. Critical haemoglobin concentration in anaesthetized dogs: comparison of two plasma substitutes. *Br J Anaesth* 1998; **81**: 556–62

96 Vaupshas HJ, Levy M. Distribution of saline following acute volume loading: postural effects. *Clin Invest Med* 1990; **13**: 165–77

97 Velanovich V. Crystalloid versus colloid fluid resuscitation: a meta-analysis of mortality. *Surgery* 1989; **105**: 65–71

98 Vermeulen LC, Ratko MA, Erstad BL, Brecher ME, Matuszewski KA. A paradigm for consensus–the university hospital consortium guidelines fo the use of albumin, nonprotein colloids, and crystalloid solutions. *Arch Intern Med* 1995; **155**: 373–9

99 Vincent JL. The colloid–crystalloid controvery. *Klin Wochensch* 1991; **69** (Suppl XXVI): S104–11

100 Vogt NH, Bothner U, Georgieff M. Comparison of human albumin 5% and 6% HES 200/0.5 as exclusive colloid component in major surgery. *Anaesthesiol Intensivmed Notfallmed Schmerzther* 1994, **29**: 150–6

101 Vogt NH, Bothner U, Lerch G, Lindner KH, Georgieff M. Large-dose administration of 6% hydroxyethyl starch 200/0.5 for total hip arthroplasty: plasma homeostasis, hemostasis, and renal function compared to use of 5% human albumin. *Anesth Analg* 1996; **83**: 262–8

102 Vogt N, Bothner U, Lerch G, Geogieff M. Pharmakokinetik und onkotisches Verhalten von hochdosierter Hydroxyethylstarke bei operativen Eingriffen im Vergleich zu Humanalbumin 5%. *Infusionsther Transfusionsmed* 1998; **25**: 212–21

103 von Sommoggy S, Frauenhofer J, Jelen-Esselborn S, Stemberger A Coagulation changes during aortofemoral bifurcation bypass operations: Plasma substitution possible with hydroxyethyl starch (HES) only? *Anaesthesist* 1990; **39**: 353–60

104 Wagner BK, D'Amelio LF. Pharmacologic and clinical considerations in selecting crystalloid, colloidal, and oxygen carrying resuscitation fluids. Part 1. *Clin Pharmacol* 1993; **12**: 335–46

105 Waldhausen P, Kiesewetter H, Leipnitz G *et al.* Hydroxyethyl starch induced transient renal insufficiency in glomerular failure. *Acta Med Austr* 1991; **18** (Suppl 1): S52–5

106 Wang P, Hauptman JG, Chaudry IH Hemorrhage produces depression in microvascular blood flow which persists despite fluid resuscitation. *Circ Shock* 1990; **32**: 307–18

107 Warren BB, Durieux ME. Hydroxyethylstarch: safe or not? *Anesth Analg* 1996; **84**: 206–12

108 Webb AR, Barclay SA, Bennett ED. *In vitro* colloid osmotic pressure of commonly used plasma substitutes: A study of the diffusibility of colloid molecules. *Intensive Care Med* 1989, **15**: 116–20

109 Webb AR. Crystalloid or colloid resuscitation. Are we any wiser? *Crit Care* 1999; **3**: R25–8

110 Weissman C. Intensive care medicine–editorial comment. *Curr Opin Anaesth* 1995; **8**: 107–8

111 Zornow MH, Prough DS. Fluid management in patients with traumatic brain injury. *New Horiz* 1995; **3**: 488–98

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SHORT COMMUNICATION

Intravenous clonidine infusion in critically ill children: dose-dependent sedative effects and cardiovascular stability

C. Ambrose, S. Sale, R. Howells, C. Bevan, I. Jenkins, P. Weir, P. Murphy and A. Wolf*

Paediatric Intensive Care Unit, Bristol Royal Hospital for Sick Children, St. Michael's Hill,
Bristol BS2 8BJ, UK

**Corresponding author*

Clonidine is used for analgesia and sedation in paediatric anaesthesia, but there are no data on its sedative properties and side effects in critically ill children. We studied 30 ventilated children aged 10 yr and under to determine an effective i.v. dosing range and to assess its cardiovascular effects. Twenty non-paralysed, ventilated children were given a background infusion of midazolam 50 μg kg^{-1} h^{-1} combined with a variable clonidine infusion (0.1–2 μg kg^{-1} h^{-1}) to maintain optimal sedation. The effects of clonidine 1 μg kg^{-1} h^{-1} on cardiac index were measured in 10 postoperative cardiac patients using a reverse Fick method. Dose-dependent sedation was achievable (713 out of 861 h) without cardiovascular side effects, but an infusion limit of clonidine 1 μg kg^{-1} h^{-1} was inadequate in two patients. An increased dose limit of 2 μg kg^{-1} h^{-1} combined with midazolam 50 μg kg^{-1} h^{-1} achieved satisfactory sedation scores for 602 out of a total of 672 h studied with no failures. Clonidine in combination with midazolam at 1 μg kg^{-1} h^{-1} was not associated with significant changes in heart rate arterial pressure or cardiac index.

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Clonidine is a lipid-soluble, partial α-2 adrenoreceptor agonist with antihypertensive, analgesic and sedative properties. Recently there has been much interest in the paediatric literature on the use of clonidine as an oral premedicant and as an adjunct to epidural blockade to provide long-lasting analgesia without ventilatory depression.[1] Data from the adult intensive care has suggested that clonidine can provide dose-dependent sedation with cardiovascular stability and a noticeable lack of drug tolerance and withdrawal.[2 3] These attributes suggest that clonidine might be a useful continuous i.v. sedative in the critically ill child, but we are not aware of any data defining a dose range or describing its use in this population. In this open dose ranging study, we set out to determine whether clonidine is an effective sedative agent in the ventilated child, to establish a clinical dose range for sedation, and to assess cardiovascular side effects.

Methods and results

With appropriate ethical approval and informed parental consent, 30 children, aged 10 yr and under were enrolled in a three-part study. Ten ventilated, unparalysed critically ill children (group 1) were sedated with a variable i.v. infusion of clonidine (0.2–1.0 μg kg^{-1} h^{-1}) together with a fixed background dose of midazolam 50 μg kg^{-1} h^{-1}. The clonidine infusion was started at 0.6 μg kg^{-1} h^{-1} in neonates and 0.8 μg kg^{-1} h^{-1} in children older than 6 months. The infusion was increased or decreased by 0.2 μg kg^{-1} h^{-1} according to the level of sedation which was measured hourly by the nursing staff using a sedation score[4] derived from the observational pain score (OPS).[5] The score ranges from 0 to 10 with optimal sedation between 2 and 7, and the clonidine infusion was adjusted to try to maintain sedation within this band. Children with a sedation score of greater than 7, despite maximal clonidine, were given an increased infusion of midazolam (100 μg kg^{-1} h^{-1}) for up to 2 h and, if sedation remained inadequate after this time, the technique was deemed to have failed. Heart rate and blood pressure were recorded as part of the routine paediatric intensive care unit (PICU) practice.

A further 10 postoperative cardiac surgical patients were

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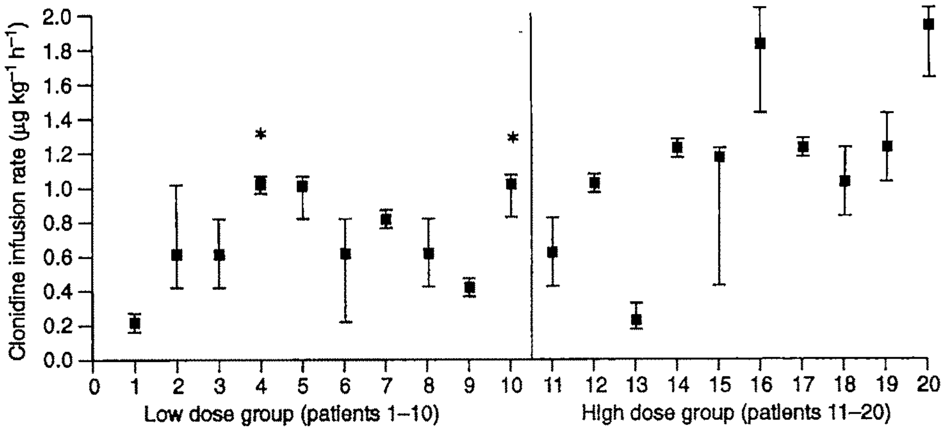

Fig 1 Median and interquartile infusion rates of clonidine needed to achieve adequate sedation using a maximum infusion of 1 (patients 1–10) or 2 $\mu g\ kg^{-1}\ h^{-1}$ (patients 11–20) Asterisks denote the failure of sedation in patients 4 and 10 in the low-dose clonidine infusion rates.

assessed for the haemodynamic effects of a fixed clonidine infusion at a rate of 1.0 $\mu g\ kg^{-1}\ h^{-1}$ specifically to determine if there were effects on cardiac index, heart rate and arterial pressure at this dose. Core and peripheral temperature were measured routinely but were not documented for the purpose of this study. These patients had central venous, pulmonary arterial and systemic arterial catheters in place which allowed trends in cardiac index to be measured using the reversed Fick method (cardiac output = oxygen demand/arteriovenous oxygen difference). Oxygen uptake was not measured, but an assumption was made that oxygen demand would be relatively fixed in these anaesthetized, paralysed but stable patients. An oxygen uptake[6] of 160 ml $min^{-1}\ m^{-2}$ was taken as a representative value in order to calculate trends in cardiac index. Most patients were receiving low-dose ionotropic support on return from theatre, but these infusions either remained at the same rate or were reduced during the 8-h study period. High-dose morphine (0.5 mg kg^{-1}) was given in a standardized fashion to all patients after separation from cardiopulmonary bypass, and a rectal dose of chloral hydrate (25 mg kg^{-1}) was given to all patients on arrival on the intensive care unit. This allowed patients to maintain adequate levels of analgesia and sedation prior to starting the clonidine infusion. Heart rate, arterial pressure and cardiac index parameters were measured immediately on returning to the intensive care unit from theatre and at 30-min intervals for 2 h before starting the clonidine infusion, and thereafter at 1-h intervals for 6 h.

Having assessed the cardiovascular safety aspects using a clonidine infusion of 1 $\mu g\ kg^{-1}\ h^{-1}$, we studied a further group of unparalysed, ventilated patients (group 2), using an identical study design to that used in the initial part of the study, but with a new maximum infusion dose of clonidine 2 $\mu g\ kg^{-1}\ h^{-1}$.

The first group of patients, in whom sedation was assessed, ranged from 7 to 38 months old (median 12.5 months). The study duration ranged from 21 to 222 h (total study time 861 h). There was large variability in the infusion rates required to achieve acceptable sedation (patients 1–10 in Fig. 1). Two patients failed to maintain adequate sedation at the maximum infusion of clonidine 1 $\mu g\ kg^{-1}\ h^{-1}$, but the other eight patients were adequately sedated (score of 2–7) for the entire study period. Using the data from the eight patients that successfully completed the study, and the data up to withdrawal for the other two patients, sedation was judged adequate for 713 of the 861 study hours (89% of the total study time). Children in group 2 receiving up to 2 $\mu g\ kg^{-1}\ h^{-1}$ clonidine were significantly younger than patients in group 1. Ages varied from 1 day to 15 months (median 2.0 months) and the individual study duration ranged from 25 to 181 h (total study 672 h). Median clonidine infusion rates for group 2 are shown as patients 11–20 in Figure 1. Adequate sedation was recorded in 602 of the 672 hourly assessments (89.5%), and there were no failures. It was clear from both groups that increasing the clonidine infusion increased the levels of sedation in a dose-dependent fashion. Bradycardia and hypotension were not recorded in any patient.

The group receiving a fixed infusion of 1 $\mu g\ kg^{-1}\ h^{-1}$ had no significant change in trends over 6 h in heart rate (166 (SD 17.9) to 154 (20.2) beat min^{-1}), blood pressure (60 (9.8) to 64 (11.1) mm Hg) or derived cardiac index (5.7 (2.2) to 6.0 (1.51) ml $m^{-2}\ min^{-1}$).

Comments

These data suggest that a variable i.v. infusion of clonidine at 0.2–2.0 $\mu g\ kg^{-1}\ h^{-1}$ in combination with a fixed low-dose infusion of midazolam, can provide dose-dependent sedation in ventilated critically ill children without adverse effects on cardiovascular performance. It is unclear whether doses greater than 2.0 $\mu g\ kg^{-1}\ h^{-1}$ of clonidine can increase sedation without significant haemodynamic effects. Morphine and midazolam are commonly used for sedation in PICU but prolonged use results in tolerance and withdrawal phenomena. In adults, clonidine is commonly used to aid opioid withdrawal and has been used as an effective alternative sedative to opioids.[3] We have now used this drug routinely in our PICU for 3 yr, as a replacement for morphine in those patients who have become tolerant to opioids or who are difficult to sedate. Ventilatory side effects, tolerance and withdrawal have not been significant features of this drug in our clinical practice even after long-term use of 7 days or more, but there are no published data to confirm this. Further substantive studies are needed to define its role within PICU and determine its side effect profile in the paediatric population.

References

1 Mishina K, Mikawa K, Shiga M, *et al.* Clonidine in paediatric anaesthesia. *Paediatr Anaesth* 1999; **9**: 187–202

2 Maze M, Tranquili W. Alpha-2 agonists: defining their role in clinical anaesthesia. *Anesthesiology* 1991; **74**: 581–605

3 Mirski MA, Muffelman B, Ulatowski JA, *et al.* Sedation for the critically ill neurological patient *Crit Care Med* 1995; **23**: 2038–53

4 Wolf AR. Neonatal analgesia. In: Rennie JM, Roberton NRC, eds. *Textbook of Neonatology*, 3rd edn. Churchill Livingstone, Edinburgh; 1999; 435–43

5 Hannallah RS, Broadman LM, Belman AB, *et al.* Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of post-orchidopexy pain in pediatric ambulatory surgery. *Anesthesiology* 1987; **66**: 832–4

6 Chang AC, Kulick TJ, Hickey PR, *et al.* Real time gas exchange measurement of oxygen consumption in neonates and infants after cardiac surgery. *Crit Care Med* 1993; **21**: 1369–75

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CASE REPORTS

Complications from regional anaesthesia for carotid endarterectomy

A. Carling* and M. Simmonds

Department of Anaesthesia, Royal Gwent Hospital, Cardiff Road, Newport, Gwent NP9 2UB, UK

**Corresponding author*

The complications of carotid endarterectomy (CEA) under cervical plexus blockade have yet to be fully evaluated. Two different cases are presented; both patients suffered sudden collapse following superficial and deep cervical plexus block in preparation for CEA. The causes, presenting signs and differential diagnoses are discussed. The safest cervical plexus anaesthetic block technique has not yet been established.

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Carotid endarterectomy (CEA) under deep and superficial cervical plexus block may be becoming more popular because of the possible overall lower incidence of morbidity and mortality.[1] A conscious patient avoids the need for transcranial Doppler, electroencephalography, evoked potentials, stump pressures, near-infrared spectroscopy and jugular venous oximetry to monitor cerebral function. The need for a shunt during cross-clamping may be reduced. At present, there is a paucity of trials that have assessed and quantified the complications from regional anaesthesia. Some of the larger trials failed to mention any anaesthesia-related complications.[2] As cervical plexus blockade becomes more widespread in its use, there is a need to be familiar with its life-threatening complications and a need to produce further clear evidence in favour of this technique.

Case 1

A 67-yr-old male patient was admitted for right carotid endarterectomy. He had suffered a left hemisphere cerebrovascular accident 9 yr previously and recurrent right amaurosis fugax. Examination revealed bilateral carotid bruits, and carotid duplex scans recorded >90% stenosis on the right and >70% stenosis on the left. He had suffered a myocardial infarction 6 yr previously but had made a good recovery and had good exercise tolerance, requiring only occasional glyceryl trinitrate. His electrocardiogram (ECG) was normal; chest x-ray showed evidence of chronic obstructive airways disease. Full blood count, clotting studies, blood glucose, urea and electrolytes were all within normal limits.

On the day of surgery he was premedicated with temazepam 10 mg orally. In the anaesthetic room i.v. access was established and a cannula inserted into the left ulnar artery. Oxygen 4 litres min^{-1} was delivered by nasal cannulae and ECG, pulse oximetry (Sp_{O_2}) and invasive blood pressure monitoring were commenced. Right deep cervical plexus block was performed using a three-injection technique as described by Lofstrom.[3] Using a 100×0.8 mm Stimuplex® needle (B. Braun, Melsungen, Germany) and a nerve stimulator, the deep cervical plexus was accurately located at three levels (C2, C3 and C4). After immobilizing the needle, aspirating to check for blood and cerebrospinal fluid, 5 ml 0.75% ropivacaine was injected at each level. This was followed by a superficial cervical plexus block in which 10 ml 0.75% ropivacaine was injected along the posterior border of the sternocleidomastoid muscle at the level of C3 using a retrobulbar needle.

Whilst completing the superficial cervical plexus block, the patient complained of feeling generally unwell and having difficulty breathing. He had no symptoms or signs of acute local anaesthetic toxicity. Within 10 min of finishing the superficial cervical plexus block he developed a transient left hemiparesis and left facial nerve palsy before becoming rapidly unconscious and apnoeic. Systolic blood pressure dropped to 60 mm Hg and the heart rate was 100 beat min^{-1}. The patient's lungs were immediately ventilated with 100% oxygen using a bag and mask, and the patient's trachea was intubated. During laryngoscopy, the gag, laryngeal and peripheral reflexes were entirely absent and no anaesthetic drugs were required. The blood pressure recovered to

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preoperative levels following 12 mg of incremental i.v. ephedrine. It was decided to postpone surgery, and 1 h after the cervical plexus block was performed the patient was transferred to the Intensive Care Unit (ICU). No sedation had been commenced at this stage.

Within 15 min of admission to the ICU, the patient abruptly woke up and started breathing. At this point it was decided to extubate the patient's trachea because he was conscious, responding to commands, had good spontaneous ventilation with Sp_{O_2} of 98–100% and was cardiovascularly stable. The patient was completely alert and oriented, and close examination revealed normal tone, power, sensation, proprioception and reflexes in all limbs, and no residual neurological deficit. The patient was discharged from the ICU and allowed home 48 h later having made a full recovery. Two subsequent computerized tomography (CT) scans showed neither evidence of new cerebral infarction nor haemorrhage. This patient continued to have recurrent episodes of amaurosis fugax and was admitted 6 weeks later and underwent a successful eversion endarterectomy of the right carotid artery under general anaesthesia.

Case 2

A 71-yr-old man presented for a right carotid endarterectomy. He had a 6-month history of intermittent slurring of the speech, and 4 months previously he had suffered sudden onset of weakness of the left arm and leg. This episode resolved completely after a week. Preoperative duplex studies revealed >90% stenosis of the right carotid artery and <50% stenosis of the left carotid artery. He also suffered from insulin-dependent diabetes mellitis complicated by diabetic retinopathy and peripheral neuropathy. He had peripheral vascular disease with intermittent claudication but no history of chronic respiratory disease. He claimed to have no angina but recently required three pillows in bed to prevent orthopnoea. Routine preoperative blood tests, ECG and chest x-ray were normal.

No premedication was prescribed. In the anaesthetic room, the patient was comfortably positioned supine and oxygen given via nasal cannulae at 4 litres min^{-1}. A left radial arterial cannula was sited. The blood pressure was 140 mm Hg systolic, pulse 100 beat min^{-1} and Sp_{O_2} 96%. A large bore i.v. cannula was sited and fentanyl 25 μg given i.v. A right superficial cervical plexus block was performed using 10 ml plain 0.5% bupivacaine. A 100×0.8 mm Stimuplex® needle and a nerve stimulator was used to locate the deep cervical plexus at four levels (C2, C3, C4, C5), and 5 ml of a mixture of 10 ml 2% lidocaine and 10 ml 0.5% bupivacaine was injected at each level. The regional blockade was technically uncomplicated.

Over a 5-min period following the last injection at C2, the patient became distressed and complained of being 'unable to breath'. The patient was noted to be hypoventilating and a progressive desaturation on pulse oximetry from 96 to 72% was observed. The systolic blood pressure increased to 170 mm Hg. There was no seizure. Following pre-oxygenation with 100% oxygen, the patient's trachea was intubated using a rapid sequence induction with etomidate 20 mg and suxamethonium 100 mg, and manual intermittent positive pressure ventilation commenced with 100% oxygen. The oxygen saturation returned to 96%. No vasopressors were required to maintain blood pressure or pulse, and following intubation the systolic blood pressure rose to 180 mm Hg and the pulse to 110 breath min^{-1}. These values returned to pre-operative levels 20 min after intubation. Between 10 and 15 min following intubation spontaneous ventilation recommenced.

The planned surgery was abandoned and the patient admitted to the ICU for continued ventilation. The patient was ventilated for a total of 110 min and then extubated uneventfully. No abnormal neurological symptoms or signs were noted on emergence from sedation and the patient's vital signs were initially stable. After extubation, over the course of the ensuing 35 min, the patient developed acute left ventricular failure, which was successfully treated using facemask oxygen, i.v. frusemide 50 mg, diamorphine 2.5 mg and an isosorbide dinitrate i.v. infusion.

The patient was discharged from the ICU 24 h later. Serial postoperative ECGs and cardiac enzymes (creatine phosphokinase MB) remained normal. A CT scan of the head performed 24 h after the collapse revealed small vessel ischaemic change and calcification of the basal ganglia, but neither evidence of a new infarction nor focal haemorrhage was seen. A repeat CT scan 2 weeks later was similar in appearance. The patient was discharged, but was readmitted 3 weeks later with a further episode of acute left ventricular failure. This was treated medically with frusemide and lisinopril and resolved. An echocardiogram performed on this occasion revealed a dilated left heart with mild/moderate mitral regurgitation and global hypokinesia.

Discussion

CEA under cervical plexus block anaesthesia may be advantageous.[1] However, we found only three case reports regarding the complications of cervical plexus block anaesthesia for CEA.[4–6] Some studies, however, have reported complications of the cervical plexus block itself, and include paroxysmal coughing, anxiety, shortness of breath, agitation, high cervical blockade,[7] hemidiaphragmatic paresis,[8] airway obstruction, seizures and tachycardia as a result of intravascular injection and drowsiness and unconsciousness from local anaesthetic toxicity.[9] Additionally, the problems of hoarseness, dysphagia, stellate ganglion block and Horner's syndrome have been highlighted.[5 10]

Brainstem anaesthesia has been reported as a complication of stellate ganglion block,[11] interscalene brachial plexus block,[12 13] parascalene brachial plexus block, and subarachnoid injection during retrobulbar block causing brainstem anaesthesia has been well documented.[14–17] Symptoms appear rapidly within 2–10 min following the block and include restlessness, vomiting, drowsiness, confusional state, cardiac depression and respiratory arrest.

There are several possible causes of collapse following cervical plexus blockade in our patients. Unconsciousness occurring 20 min after cervical blockade has been reported previously but the details are scanty.[9] Local anaesthetic toxicity was the presumed mechanism. In both cases presented here, neither seizures typical of local anaesthetic toxicity from inadvertent injection into the vertebral artery nor central nervous system excitation from rapid inadvertent i.v. injection were observed, and the lateralizing neurological signs observed in case 1 would not be characteristic of toxicity.[18] Furthermore, ropivacaine has a lower potential for toxicity which makes it a very suitable agent for cervical plexus anaesthesia.[19] [20] The total dose of ropivacaine given (187.5 mg) was below the manufacturer's dose guidelines (225–300 mg). The subsequent CT scans of the brain in both patients excluded acute cerebral infarction and haemorrhage. In case 1, the rapid loss of consciousness, absence of brainstem reflexes on laryngoscopy, apnoea, hypotension and full neurological recovery supports the diagnosis of acute brainstem anaesthesia. The lateralizing neurological signs that presented early in this patient's collapse are not characteristic of brainstem anaesthesia, and transient cerebral ischaemia secondary to hypotension is a more likely explanation for the transient hemiparesis. Winnie has described three ways that local anaesthetic agents can cause a subarachnoid block during a brachial plexus block, and it is reasonable to assume that these mechanisms hold true for a cervical plexus block.[21] Firstly, the needle may be inserted directly through the intervertebral foramina and the anaesthetic agent injected directly intrathecally. Second, the tip of the needle may enter a dural cuff that sometimes accompanies a nerve for a short distance distal to the intervertebral foramina, causing a direct intrathecal injection. Third, local anaesthetics injected into the nerve itself can spread centripetally to the subarachnoid space. In case 1, no cerebrospinal fluid was aspirated before injection and there was no delayed headache, although this does not necessarily preclude the possibility of dural puncture. No pain was elicited on injection, making a direct intraneural injection unlikely. It is reasonable to speculate that the mechanism of brainstem anaesthesia was accidental injection into a dural cuff[22]

A meticulous technique involving careful positioning of the needle with caudal angulation, accurate location of the cervical plexus using nerve stimulation, needle immobilization and careful aspiration before slow injection of the local anaesthetic agent, as performed in these cases, does not guarantee that brainstem anaesthesia will be avoided. The administration of a small test dose at each injection site would require a wait of several minutes before the administration of the main dose to check for the possibility of brainstem anaesthesia, and in practice this would be cumbersome and impractical. It is therefore imperative that anaesthetists performing this technique are fully aware and prepared for this rare complication. Factors associated with cervical block include: ill-defined anatomy of the neck and cervical spine; obesity; inability to position the patient correctly; poor patient cooperation; repeated needling before finding the correct position; failure to carefully aspirate for blood or cerebrospinal fluid; and rapid injection of local anaesthetic agent.[23] None of these risk factors was present in either case.

There is no clear evidence that a single injection technique for cervical plexus blockade is safer than the three-injection technique or vice versa, but it is clearly necessary to compare different techniques for safety and complications.[24] Although accidental brainstem anaesthesia with cervical blockade is a rare event, further study should be undertaken to verify the safest technique to reduce the risk of this particular complication.

The diagnosis in case 2 at the time of presentation was not so clear. There was no rapid loss of consciousness, no significant hypotension, and tracheal intubation required anaesthesia and muscle relaxation which excludes brainstem anaesthesia. No sensory or motor signs were noted in the upper limbs and Horner's syndrome was not seen, making a diagnosis of an accidental epidural injection unlikely.[25] Left ventricular failure at the time of the block may be a cause of hypoventilation and desaturation, but in case 2 this would have been exacerbated by possible phrenic nerve paralysis. Diaphragmatic motion abnormalities have been demonstrated previously in 61% of patients receiving cervical plexus blocks, and respiratory distress due to phrenic nerve palsy following deep cervical blockade has already been reported in a patient with chronic respiratory disease.[5] [8] The most likely diagnosis in case 2 is cardiorespiratory failure exacerbated by a possible phrenic nerve paresis in a patient with pre-existing poor left ventricular function. It has been previously highlighted that cervical plexus block should be used with great care in patients with pre-existing chronic respiratory disease, but our case report highlights the need for caution in patients with left ventricular failure.

Although deep cervical plexus block for CEA has advantages, anaesthetists need to be constantly vigilant when performing this procedure, and more willing to report and study the related complications.

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References

1 Stoneham MD, Knighton JD. Regional anaesthesia for carotid endarterectomy. *Br J Anaesth* 1999; **82**: 910–19

2 Fiorani P, Sbarigia E, Speziale F, *et al.* General anaesthesia versus cervical blockade and perioperative complications in carotid artery surgery. *Eur J Vasc Endovasc Surg* 1997, **13**. 37–42

3 Lofstrom B Cervical nerve block. In. Eriksson E, ed. *Illustrated*

Handbook in Local Anaesthesia, 2nd edn. London: Lloyd-Luke, 1979; 77–8

4 Goldberg MJ. Complication of cervical plexus block or fugue state? *Anesth Analg* 1995; **81**: 1108–9

5 Stoneham MD, Wakefield TW. Acute respiratory distress after deep cervical plexus block. *J Cardiothorac Vasc Anesth* 1998; **12**: 197–8

6 Szocik JF, Kellogg W, Wakefield TW. Temporary facial nerve palsy during carotid endarterectomy under local anesthesia. *Anesth Analg* 1995; **81**: 1106–7

7 Lawrence PF, Alves JC, Jicha D, Bhirangi K, Dobrin PB. Incidence, timing and causes of cerebral ischemia during carotid endarterectomy with regional anesthesia. *J Vasc Surg* 1998; **27**: 329–34

8 Castresana MR, Masters RD, Castresana EJ, Stefansson S, Shaker IJ, Newman WH. Incidence and clinical significance of hemidiaphragmatic paresis in patients undergoing carotid endarterectomy during cervical plexus block anesthesia. *J Neurosurg Anesthesiol* 1994; **6**: 21–3

9 Davies MJ, Silbert BS, Scott DA, Cook RJ, Mooney PH. Superficial and deep cervical plexus block for carotid artery surgery. A prospective study of 1000 blocks. *Reg Anesth* 1997; **22**: 442–6

10 Castresana MR, Brooks AG, Masters RD, Castresana EJ, Myers GJ, Newman WH. Incidence of dysphagia in patients undergoing carotid endarterectomy using deep and superficial cervical plexus block anesthesia. *Anesth Analg* 1994; **78**: S52

11 Whitehurst L, Harrelson JM. Brain-stem anaesthesia. An unusual complication of stellate ganglion block. *J Bone Joint Surg (Am)* 1977; **59-A**: 541–2

12 Ross S, Scarborough CD. Total spinal anaesthesia following brachial-plexus block. *Anesthesiology* 1973; **39**: 458

13 Edde RR, Deutsch S. Cardiac arrest after interscalene brachial-plexus block. *Anesth Analg* 1977; **56**: 446–7

14 Baraka A, Hanna M, Hammoud R. Unconsciousness and apnea complicating parascalene brachial plexus block: possible subarachnoid block. *Anesthesiology* 1992; **77**: 1046–7

15 Tatum PL, Defalque RJ. Subarachnoid injection during retrobulbar block: a case report. *Am Assoc Nurse Anesth J* 1994; **62**: 49–52

16 Mercereau DA. Brain stem anesthesia complicating retrobulbar block. *Can J Ophthalmol* 1989; **24**: 159–61

17 Morgan GE. Post-retrobulbar apnea syndrome. *Reg Anesth* 1989; **14**: 203–5

18 Kozody R, Ready LB, Barsa JE, Murphy TM. Dose requirement of local anaesthetic to produce grand mal seizure during stellate ganglion block. *Can Anaesth Soc J* 1982; **29**: 489–91

19 Knudsen K, Beckman Suurkula M, Blomberg S, Sjovall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997; **78**: 507–14

20 Leoni A, Casati A, Fanelli G, Aldegheri G, Casaletti E, Torri G. A double-blind comparison between 0.75% ropivacaine and 2% mepivacaine for axillary brachial plexus anaesthesia. *Anaesth* 1998; **53**(Suppl 2): 92

21 Winnie AP. Considerations concerning complications, side effects and untoward sequelae. In: Hakansson L, ed. *Plexus Anaesthesia: Perivascular Techniques of Brachial Plexus Block*. Philadelphia: WB Saunders, 1983; 221–65

22 Norris D, Klahsen A, Milne B. Delayed bilateral spinal anaesthesia following interscalene brachial plexus block. *Can J Anaesth* 1996; **43**: 303–5

23 Checketts MR, Wildsmith JAW. Accidental i.v. injection of local anaesthetics: an avoidable event? *Br J Anaesth* 1998; **80**: 710–1

24 Winnie AP, Ramamurthy S, Durrani Z, Radonjic R. Interscalene cervical plexus block: a single-injection technic. *Anesth Analg* 1975; **54**: 370–5

25 Scammell SJ. Inadvertent epidural anaesthesia as a complication of interscalene brachial plexus block. *Anaesth Intens Care* 1979; **7**: 56–7

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Transthoracic echocardiography for perioperative haemodynamic monitoring

M. Filipovic[1] *, M. D. Seeberger[1], M. C. Schneider[1], M. Schmid[1], H. Pargger[1], P. Hunziker[2] and K. Skarvan[1]

[1]Department of Anaesthesia and [2]Department of Internal Medicine (Division of Cardiology), University of Basel, CH-4031 Basel, Switzerland

**Corresponding author*

Transoesophageal echocardiography (TOE) is valuable for perioperative monitoring in patients at risk from haemodynamic disturbance. However, its use is not practicable in patients undergoing surgical procedures under regional anaesthesia. We describe two cases showing that transthoracic echocardiography (TTE) has the same advantages as TOE and thus may be valuable for monitoring awake patients. TTE should be considered when extended perioperative haemodynamic monitoring is needed but TOE is not possible.

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Transoesophageal echocardiography (TOE) is valuable for perioperative monitoring in patients at risk for haemodynamic disturbance.[1] When regional anaesthesia is chosen, as is often the case in patients undergoing Caesarean delivery, TOE is impracticable. We report two cases showing that transthoracic echocardiography (TTE) can image the heart during surgery and may be an alternative method of monitoring in such patients.

Case 1

A 34-yr-old, gravida 1, nulliparous woman was admitted at 15 weeks gestation with symptoms of congestive heart failure. She had no history of cardiovascular disease and early pregnancy was uneventful. TTE assessment showed dilated cardiomyopathy of unknown origin with impaired left ventricular (LV) systolic function (fractional shortening 21%) and bilateral pleural effusions. Despite treatment with digoxin, diuretics, nitrates and dihydralazine, orthopnoea and shortness of breath increased and fractional shortening decreased to 12%. Therefore, an urgent Caesarean delivery was planned at 32 weeks' gestation. No signs of foetal distress were present.

After arterial and central venous pressure monitoring had been started, a combined spinal–epidural anaesthesia (CSEA) technique was performed. Intrathecal injection of 0.5% hyperbaric bupivacaine 7.5 mg, fentanyl 10 μg and morphine 0.25 mg, supplemented by 0.5% bupivacaine 55 mg injected epidurally resulted in a T6 sensory level. At onset of anaesthesia, systolic arterial blood pressure transiently decreased from 140 to 85 mm Hg but then became steady around 95 mm Hg.

Baseline TTE (2.0/2.5 MHz probe, Sonos 2500, Hewlett Packard, Andover, MA, USA), which included parasternal long- and short-axis and apical four- and two-chamber views, was done before starting anaesthesia. The examination confirmed the preoperative findings of poor LV function and showed a fresh thrombus in the apex of the left ventricle, which had not been seen before (Fig. 1). As soon as CSEA had been started, LV dimensions and LV function (fractional shortening) were monitored in the parasternal long-axis view to control the effect of CSEA and to guide the quantity and speed of fluid replacement and administration of vasoactive drugs. The continuous qualitative assessment was supplemented by repeated quantitative measurements of LV end-diastolic and end-systolic dimensions and LV shortening fraction (Fig. 2). The strategy was to give intravenous fluids when arterial blood pressure and LV diastolic dimension decreased simultaneously, and to give vasoactive drugs when arterial pressure decreased without changes in LV diastolic dimension or with an increase in LV systolic dimension (i.e. worsening of systolic function).

After starting CSEA, LV diastolic dimension decreased without changes in systolic shortening (Fig. 2), and the patient's shortness of breath improved. These observations were interpreted as a reduction in pre-existing hypervolaemia, and only minimal fluid was given. An estimated blood loss of 600 ml was replaced with 600 ml lactated

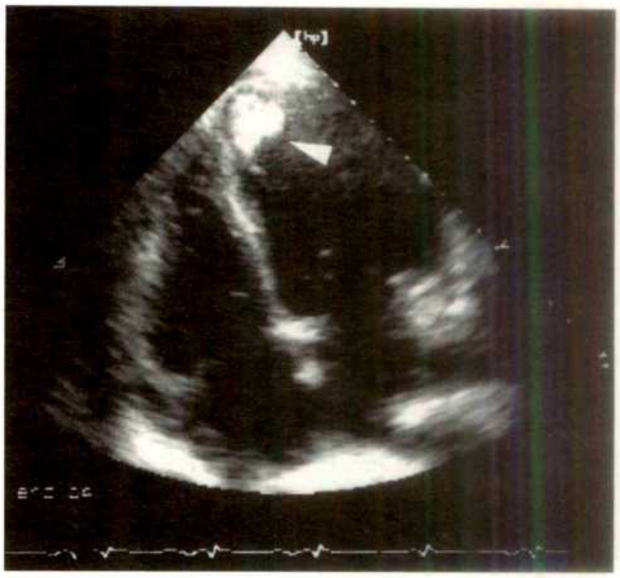

Fig 1 TTE of the patient of Case 1. Four-chamber view with apical thrombus in the left ventricle (arrowhead).

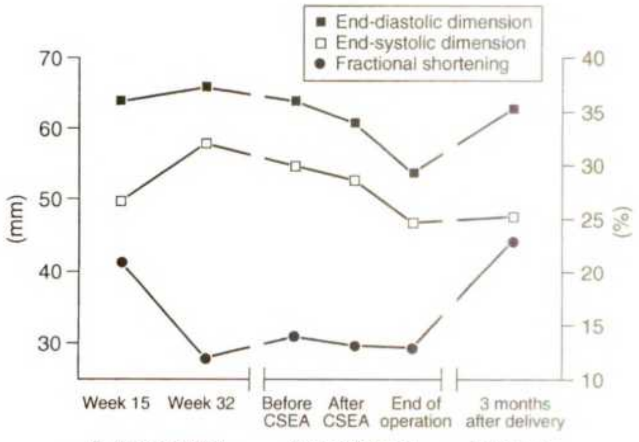

Fig 2 Course of end-diastolic and end-systolic dimensions and fractal shortening in the patient of Case 1.

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Ringer's solution, and a transient decrease in arterial blood pressure was treated with phenylephrine 100 μg.

Neonatal outcome was excellent. On the first postoperative day, the epidural catheter was removed after administration of morphine 3 mg. Anticoagulant therapy with heparin followed by coumarin was subsequently started.

The cardiological follow-up visit 3 months after delivery showed unchanged LV dimensions but improved LV function (fractional shortening 23%) (Fig. 2). The LV thrombus had disappeared and anticoagulant therapy was stopped.

Case 2

A 32-yr-old, gravida 3, para 2 woman was admitted at 39 weeks' gestation because of known cardiac disease. Six years before, bacterial endocarditis had caused severe mitral insufficiency needing surgical closure of a perforation in the posterior leaflet of the mitral valve.

The course of the actual pregnancy was uneventful and without any sign of congestive heart failure. Because of a systolic murmur, TTE was performed and showed severe mitral insufficiency, dilatation of the left atrium and left ventricle but preserved LV systolic function (fractional shortening 35%). An elective Caesarean delivery was planned. No signs of foetal distress were present.

After arterial and central venous pressure monitoring had been started, CSEA was given. Intrathecal injection of 0.5% hyperbaric bupivacaine 7.5 mg resulted in a T4 sensory level. At onset of anaesthesia, systolic blood arterial pressure transiently decreased from 125 to 90 mm Hg but then became steady around 120 mm Hg.

A complete TTE examination (2–4 MHz probe S4, Sonos 5500) was done when the patient came to the operating theatre. As soon as CSEA had been started, LV dimensions and function and the grade of mitral regurgitation were monitored continuously in the four-chamber view. The grade of mitral regurgitation was assessed semiquantitatively by comparing the area of colour Doppler jet with the left atrial area and the propagation of the jet into the left atrium. The management plan concerning fluids and the vasoactive drugs was the same as described in Case 1. The TTE guided haemodynamic management lactated Ringer's solution 2300 ml and hetastarch 500 ml, giving ephedrine 15 mg) caused no relevant changes in LV size or mitral regurgitation. The estimated blood loss was 600 ml.

Neonatal outcome was excellent. Postoperative analgesia was done by epidural administration of 0.1875% bupivacaine at the rate of 6 ml h^{-1}. On postoperative day one, the patient was in excellent clinical condition and TTE showed a smaller LV. After decreasing bupivacaine administration on day 2, the patient became dyspnoeic and oxygen saturation decreased to 88%. Clinical and radiological examination revealed acute pulmonary oedema.

After starting therapy with angiotensin-converting enzyme inhibitors, nitrates and diuretics, the patient's condition improved rapidly and she was discharged on the 10th postoperative day.

Discussion

According to the Practice Guidelines for Perioperative Transoesophageal Echocardiography, an increased risk of haemodynamic disturbance during the perioperative period is a category-II indication for perioperative TOE, indicating that 'TOE may be useful in improving clinical outcomes'.[1] Our two patients fulfilled these criteria, but the use of TOE was not feasible because they were awake. Regional anaesthesia was chosen because it is advantageous in patients undergoing Caesarean delivery who are at increased risk of aspiration of gastric contents.[2]

We show that TTE can be used instead of TOE for extended non-invasive haemodynamic monitoring in awake surgical patients, although the quality of the image may be more variable with TTE. TTE facilitated appropriate guidance of volume replacement and use of vasoactive drugs.

In Case 1, the echocardiographic finding of a decrease in LV end-diastolic dimension with unchanged systolic function after initiation of CSEA (Fig. 1), with a simultaneous decreased shortness of breath, led to the decision to replace blood loss only partially. In addition, the detection of a previously unknown LV thrombus markedly altered postoperative management.

In Case 2, echocardiographic findings contributed crucially to the decision to administer fluids in order to compensate for vasodilation caused by sympathetic blockade[3] and for blood loss. Fluid replacement would have been stopped had LV dimensions increased, LV function worsened or mitral regurgitation increased.

As an alternative to TTE monitoring, we considered the use of a pulmonary artery catheter, which has been suggested for patients with significant cardiovascular disease who are at risk of haemodynamic disturbance.[4] We decided against this because (1) it is more invasive than TTE, (2) echocardiography can provide superior information in haemodynamically unstable patients,[5–7] and (3) direct visualization of the heart can provide clinically important new information (as with the thrombus in Case 1). Moreover, in critically ill patients the use of a pulmonary artery catheter has been associated with increased mortality in a recent study.[8] In addition, using the same diagnostic technique before, during and after surgery can improve assessment of the course of the cardiac disease (Fig. 2). The importance of postoperative cardiovascular monitoring in cardiac risk patients is emphasized by the onset of acute pulmonary oedema on the second day, probably caused by reducing the epidural bupivacaine administration, decreasing the sympathetic blockade and increasing LV pre- and afterload.

TTE can be useful for non-invasive perioperative haemodynamic monitoring in patients with severe cardiac disease, and should be considered if extended perioperative haemodynamic monitoring is indicated but the use of TOE is impossible.

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References

1 Task Force on Perioperative Transesophageal Echocardiography. Practice guidelines for perioperative transesophageal echocardiography. *Anesthesiology* 1996; **84**: 986–1006
2 Santos AC, Pederson H, Finster M. Obstetric anesthesia. In: Barasch PG, Cullen BF, Stoelting RK, eds. *Clinical Anesthesia*. 3rd edn. Philadelphia: Lippincott-Raven, 1996: 1068–70
3 Lewis M, Thomas P, Wilkes RG. Hypotension during epidural analgesia for Caesarean section. Arterial and central venous pressure changes after acute intravenous loading with two litres of Hartman's solution. *Anaesthesia* 1983; **38**: 250–3
4 Practice guidelines for pulmonary artery catheterization. A report by the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization. *Anesthesiology* 1993; **78**. 380–94
5 Sohn DW, Shin GJ, Oh JK, *et al.* Role of transesophageal echocardiography in hemodynamically unstable patients. *Mayo Clin Proc* 1995; **70**: 925–31
6 Reichert CL, Visser CA, Koolen JJ, *et al.* Transesophageal echocardiography in hypotensive patients after cardiac operations. Comparison with hemodynamic parameters. *J Thorac Cardiovasc Surg* 1992; **104**: 321–6
7 Fontes ML, Bellows W, Ngo L, Mangano DT Assessment of ventricular function in critically ill patients: limitations of pulmonary artery catheterization. Institutions of the McSPI Research Group. *J Cardiothorac Vasc Anesth* 1999; **13**: 521–7
8 Connors AF Jr, Speroff T, Dawson NV, *et al.* The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *J Am Med Assoc* 1996, **276** 889–97

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Successful resuscitation from recurrent ventricular fibrillation secondary to butane inhalation

K. E. Edwards* and R. Wenstone

Intensive Care Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool, UK
**Corresponding author*

Resuscitation from cardiac arrest caused by volatile substance abuse is rarely successful. Large doses of catecholamines given during resuscitation, in the presence of butane, may cause recurrent ventricular fibrillation. We report a case of prolonged resuscitation in a young man who had inhaled butane. Cardiac output was restored 10 min after the administration of intravenous amiodarone. We suggest that antiarrhythmic agents should be used early during resuscitation to prevent recurrent arrhythmias.

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Volatile substance abuse (VSA) may be defined as the deliberate inhalation of a volatile substance to achieve a change in mental state.[1] VSA is an important cause of death in those under 20 yr of age. In 1997, VSA accounted for 1 in 50 of all deaths (or 1.7 deaths per 100 000 population) in people aged 15–19 yr in the UK. Most of the deaths are caused by inhaled gas fuels. In 1997, 56% of all VSA deaths in the UK were associated with butane.[2] Butane is found mainly in cigarette lighter refills and is used as an aerosol propellant.

Case report

A 17-yr-old male with a 3-yr history of butane abuse was found collapsed in the street. By his side was a canister of butane lighter fuel. When the paramedical emergency team arrived he was in ventricular fibrillation (VF). They gave two cycles of the advanced cardiac life support protocol, which included epinephrine 2 mg. On arrival in the emergency department he had a carotid arterial pulse that was just palpable. He then developed VF again. Advanced life support continued for a further 40 min. During resuscitation

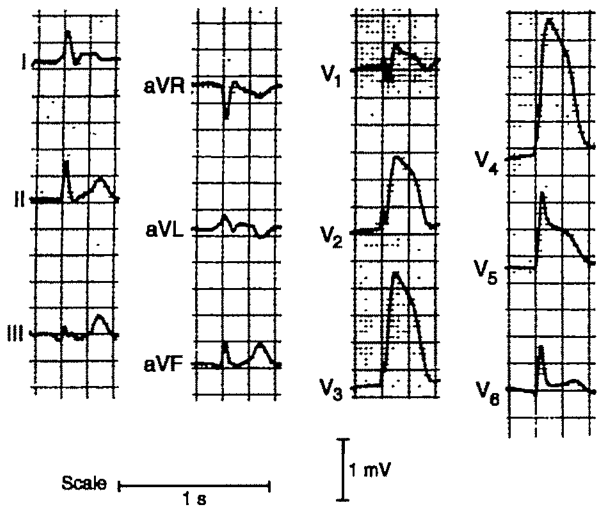

Fig 1 ECG showing an acute anterolateral myocardial infarction.

he received epinephrine 16 mg, 8.4% sodium bicarbonate 150 ml, lidocaine 50 mg, 0.9% sodium chloride 3 litres and 27 DC shocks. After amiodarone 300 mg i.v. had been given, sinus rhythm was detected but no pulses were felt. Advanced cardiac life support continued and 10 min later a pulse was felt. Heart rate was 120 min^{-1} and arterial pressure was 130/70 mm Hg. There was no spontaneous respiratory effort. He was unresponsive to pain and the pupils were dilated and unreactive to light. His temperature was 35°C. Arterial blood gas analysis showed pH 7.22, $P\text{o}_2$ 67.3 kPa, $P\text{co}_2$ 6.2 kPa and a base deficit of 9.2 mmol litre^{-1} while he was being manually ventilated with a resuscitation system supplied with oxygen at 15 litre min^{-1}. Other investigations were: carboxyhaemoglobin 1.7%, blood alcohol <1 mmol litre^{-1}, serum potassium 5.4 mmol litre^{-1} and magnesium 0.85 mmol litre^{-1}. Urine testing was negative for benzodiazepines, amphetamines, cocaine metabolites, cannabinoids, opiates and methadone. A head CT scan showed no abnormality and ECG showed an acute anterolateral infarction (Fig. 1). Plasma cardiac troponin T concentration 12 h later was 27 μg litre^{-1} (normal level, <0.10 μg litre^{-1}).

The patient was admitted to the intensive care unit, where he remained cardiovascularly unstable, with a heart rate of 150 min^{-1} sinus rhythm, arterial blood pressure of 50/20 mm Hg and central venous pressure of 10 mm Hg. Arterial blood pressure did not improve after 4.5% human albumin solution 500 ml had been given, but central venous pressure increased to 15 mm Hg. After an infusion of norepinephrine had been started, the mean arterial pressure increased to 90 mm Hg and heart rate decreased to 110 beat min^{-1}.

Four and a half hours after restoration of cardiac output, the pupils started reacting to light and sedation was required to allow mechanical ventilation.

The following morning (13 h after restoration of cardiac output) a pulmonary artery floatation catheter was inserted uneventfully. The initial studies were as follows: cardiac index = 2.28 litre min^{-1} m^{-2} (range 2.8–3.5), central venous pressure = 18 mm Hg, pulmonary artery occlusion pressure = 20 mm Hg, systemic vascular resistance index = 2900 dyne s cm^{-5} m^{-2} (range 1700–2600). The norepinephrine was stopped and an epinephrine infusion was started. Episodes of ventricular tachycardia occurred and an amiodarone infusion was also started.

Subsequent recovery was slow and complicated by acute renal failure requiring haemodialysis and recurrent pulmonary oedema. Echocardiography showed a hypokinetic apex and ventricular septum. Fractional shortening was 23%.

At 3 months no neurological deficit was found. Renal function recovered but creatinine clearance was reduced (33 ml min^{-1}). Echocardiography showed an apical aneurysm and good left ventricular function. He continues to abuse volatile substances.

Discussion

Sudden death after inhalation of volatile substances can have a number of mechanisms, including central respiratory depression and hypoxia, vagal stimulation causing asystole and myocardial sensitization to catecholamines resulting in VF.[3]

Acute inhalation of hydrocarbons such as butane can cause epinephrine-induced cardiac arrhythmias, particularly if myocardial ischaemia is present.[4] Animal studies show that myocardial sensitivity can persist for hours after inhalant exposure.[5] A previous review suggested that high doses of epinephrine in cases of VF secondary to volatile substance abuse may be harmful and cause recurrent VF.[3] We suggest that this patient developed a primary or secondary VF arrest which was initially terminated by DC shock. The recurrence of VF may have been initiated by myocardial ischaemia or infarction, but large doses of catecholamines and the butane could have decreased the threshold for arrhythmias.

Shortly after i.v. amiodarone, sinus rhythm and a cardiac output were restored. Amiodarone is a class 3 antiarrhythmic agent. It blocks potassium channels, thus increasing the duration of the action potential in the conducting system and myocardium. Repolarization is delayed and the maximum rate of repolarization is decreased. Ventricular activity from enhanced automaticity, re-entry or pathological afterpotentials is suppressed.[6] It has the advantage of causing little or no myocardial depression. Adgey and colleagues recommend administering β-adrenergic antagonists to protect the catecholamine-sensitized heart.[3] However, these agents have a negative inotropic effect and should be used with care. Other treatments that could have been considered include bretylium or further lidocaine. Bretylium can cause hypotension and vasodilatation. The main value of lidocaine is its ability to prevent ventricular arrhythmias. Its role in assisting defibrillation is less certain.

Giving 3 litres of 0.9% sodium chloride during immediate resuscitation could have been unwise, but at this stage the cause of cardiac arrest was not clear. Hypovolaemia was a potential problem. After equilibration between interstitial and intravascular compartments, this would cause an increase in intravascular volume of about 1 litre.

This patient had significant renal and myocardial damage but no apparent neurological deficit. This may indicate differences in oxygen extraction and consumption in these organs during resuscitation. Butane could perhaps exert a neuroprotective effect.

The patient had a large anterior myocardial infarction and developed an apical aneurysm. A similar event has been reported after inhalation of contact adhesive, the postulated mechanism being coronary artery spasm.[7]

Survival after cardiac arrest resulting from volatile substance abuse is unusual as most cases are unwitnessed. We believe that this is the first report of survival from a prolonged VF arrest secondary to butane inhalation with a good neurological outcome.[8] In similar cases, the early use of antiarrhythmic agents such as amiodarone should be considered.

References

1 Advisory Council On The Misuse Of Drugs. *Volatile Substance Abuse*. London: HMSO, 1995

2 Taylor JC, Norman CL, Bland JM, *et al. Trends in Deaths Associated With Abuse of Volatile Substances 1971–1997*. London· Department of Public Health, St George's Hospital Medical School, 1999

3 Adgey J, Johnson P, McMechan S. Sudden cardiac death and substance abuse. *Resuscitation* 1995; **29**: 219 – 221

4 Flowers NC, Horan LG. Nonanoxic aerosol arrhythmias. *JAMA* 1972; **19**: 33–7

5 Taylor GJ, Harris WS. Cardiac toxicity of aerosol propellants. *JAMA* 1970; **214**: 81–5

6 Calvey TN, Williams NE. Antiarrhythmic and antianginal drugs. In: *Principles and Practice of Pharmacology for Anaesthetists*. Oxford· Blackwell Science, 1997; 505–35

7 Cunningham SR, Dalzell GWN, McGirr P, Khan MM. Myocardial infarction and primary ventricular fibrillation after glue sniffing. *BMJ* 1987; **294**: 739–40

8 Williams DR, Cole SJ. Ventricular fibrillation following butane gas inhalation. *Resuscitation* 1998; **37**: 43–5

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Management of complications of tracheal surgery—a case of dehiscence

C. D. Rigg[1], I. D. Conacher*, M. L. Paes and C. J. Hilton

Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK
[1]Present address: Hull Royal Infirmary, Hull, UK
**Corresponding author*

We report a case of tracheal stenosis in a patient with immune thrombocytopenia who presented 4 yr after splenectomy. The 20-yr progression of the stenosis and management, including resection, is charted. The period after resection was complicated by wound infection, surgical emphysema, mediastinitis and dehiscence of the anastomosis of the trachea. The management of patients with tracheal lesions is discussed, but concentrates on airway care after tracheal resection when complications developed. A laryngeal mask airway was used to stabilize an uncuffed tracheal tube at the site of dehiscence.

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Tracheal stenosis is a rare complication associated with tracheal intubation.[1] The need to share a compromised airway during surgical management is a major problem for anaesthetists, and the possible unusual, severe, even catastrophic complications have implications for those involved in postoperative care. The progress of a patient, in whom a stenosis was caused by a single short period of tracheal intubation 20 yr before, is illustrative.

Case report

The female patient was referred in 1982 at the age of 21. She gave a 2–3 yr history of noisy breathing, particularly on exertion and with respiratory tract infections. She was asymptomatic with normal activity, but shortness of breath occurred on moderate to severe exertion. Previously, she had a Ramstedt's pyloromyotomy for infantile pyloric stenosis, and, 3 yr before presentation, had a splenectomy for idiopathic thrombocytopenia. On examination, she had mild stridor on forced inspiration and expiration. Reduced lung volumes and flow volume loops suggested moderately severe extra-thoracic, large airway obstruction. At rigid bronchoscopy, a stenosis was found 2 cm below the vocal cords which reduced the tracheal lumen by ~50%. This was dilated with bougies until a small adult bronchoscope could be passed easily. Symptomatically, she was improved.

In response to the periodic development of symptoms (increasing dyspnoea), she underwent a further seven rigid bronchoscopic dilatations over the next 10 yr. By 1991, bronchoscopic dilatation was required with increasing frequency. Stridor and dyspnoea were more severe, and she was having difficulty expectorating. A second stricture had developed. Carbon dioxide laser treatment was attempted as well as the usual dilatations.

Over the next 2 yr, her condition deteriorated. Three areas of tracheal narrowing were seen on a nuclear magnetic resonance tomogram. The first was located 4 cm below the vocal cords, extended 2–4 cm centrally and reduced the lumen to 0.5 cm. A second was located at the level of the third thoracic vertebrae. A third was at the entrance to the left main bronchus. It was felt that tracheal resection was indicated.

The operation was performed through a cervical incision that was extended over the upper sternum. A 5-cm length of trachea was resected and the trachea reanastomosed end-to-end. A total i.v. technique of anaesthesia was used with propofol, atracurium for neuromuscular block, and additional administration of fentanyl and morphine. The airway was secured with a 6.0-mm reinforced, cuffed oral tracheal tube with the tip beyond the main narrowing. During dissection and resection around the tube, a jet ventilator[2] was used. At the end of surgery, her head was held in flexion with a restraint and by suturing her chin to her chest. She was transferred to the intensive care unit, intubated, sedated and was ventilated for 12 h with a Penlon high-frequency jet ventilator at a rate of 100 per min and a driving pressure of 15 psi. She was extubated the following day.

On postoperative day 6, wound dehiscence occurred close to the site of the tracheal anastomosis and she developed surgical emphysema and signs of mediastinitis. She was reintubated, conventional positive pressure ventilation was started, and repeated courses of antibiotics prescribed. On day 10, the wound was explored. A large air leak developed and mechanical ventilation of the lungs became impossible. Rigid bronchoscopy was performed. A defect involving 30% of the tracheal diameter at the site of the anastomosis was seen with copious secretions beyond. With the rigid bronchoscope in position, and ventilation with a Sanders injector, it proved possible to debride the wound and anastomosis. A naso-gastric tube was passed, and a naso-pharyngeal suction system established. A tracheostomy tube through the wound into the trachea proved too long and unreliable, so a 6.0-mm cuffed oral tracheal tube was placed central to the defect under direct vision through the wound and the wound packed with providone iodine on gauze. The tube proved satisfactory for a time but because of the short trachea remnant, the cuff obstructed the right main bronchus, precipitating several short hypoxic incidents. It was also thought that the inflated cuff would further contribute to the delay in the healing of the trachea.

Clearly, the position of the tip of the tracheal tube was critical. Once again, the airway was secured central to the anastomosis with a rigid bronchoscope. A bougie was passed into the trachea through the bronchoscope and 5.0-mm uncuffed, microlaryngeal tube (MLT) 'rail-roaded' into position. In order to support and splint the tube, a size 3, laryngeal mask airway (LMA), shortened by 7 cm, was 'rail-roaded' over it and the cuff inflated with 20 ml of air. The cuff of the LMA was deflated for 5 min h^{-1} to lessen the risk of pressure trauma to the pharynx.

HFPPV was recommenced via the MLT and continued for 6 days. Plastic surgery reconstruction of the trachea was then conducted using pectoralis major muscle flaps. After a further 5 days, using the same airway and ventilation system, it was possible to dispense with the LMA and insert a cuffed 7.0-mm tracheal tube to allow conventional weaning. On day 27, she was discharged from the ITU and returned home 4 weeks later with a residual left vocal cord palsy and a small tracheo-cutaneous sinus which was left to close spontaneously.

A month later, she presented with respiratory distress due to further tracheal narrowing and had a tracheal stent inserted. To date, she has required several further admissions for rigid bronchoscopy, insertions of tracheal stents and for dilatation, one of which was complicated by a pneumothorax. Her day-to-day activities are restricted and her lung function tests are now 50% of predicted. The left main bronchus, now almost extrathoracic, is severely narrowed and has recently become impossible to cannulate with a bronchoscope though it continues to be possible to dilate it with a gum elastic bougie.

Discussion

Postintubation lesions continue to be the principal indication for tracheal resection and reconstruction[1] though the prevalence has been reduced since the 1980s when the use of tracheal and tracheostomy tubes with high-volume, low-pressure cuffs became routine. The aetiology of the stenosis in this case is speculative, but there is a clear temporal association with the splenectomy operation. It has not proved possible to find the details of the anaesthetic for that occasion but there is no suggestion that any untoward events, such as hypotension, occurred or that the procedure was complicated or prolonged. However, given the era, it is likely that a high-pressure cuff tube was used and possible that it would have been of red rubber. Because of the rarity of this complication, even when red rubber tubes were routine, and its aggressive nature, we consider that the background problem of the idiopathic thrombocytopenia, and the concomitant use of steroids,[1] are likely factors in the pathogenesis and her propensity to develop airway stenoses following minor and uncomplicated instrumentation.

The therapeutic options for patients who were symptomatic with benign airway lesions were dilatation and surgery.[1] Later, lasers were used but largely now are discredited for benign inflammatory lesions because of the potential to increase the scarring and only indicated when strictures are web-like. Tracheo-bronchial stents and balloon dilatation are more recent therapeutic developments.[3 4]

For this patient, periodic rigid bronchoscopy and bougie dilatation proved adequate for many years and were enough to tide the patient through an uncomplicated general anaesthetic for a Caesarean section. A Caesarean section, after her tracheal resection, was conducted without problem with a spinal anaesthetic. The use of a rigid bronchoscope to resolve the various conflicts between operator and anaesthetist in the airway has been fundamental to techniques that have been developed locally for managing central airway problems.[5] These include mediastinal masses and malignant disease, and for dilatations, cryotherapy, lasers, stent insertion and, as in this case, times when a tracheostomy is not an option and more expedient solutions are contemplated.

Surgery was proposed when her problems became severe because the technology of stenting was not well advanced. Good results are reported in 90% of cases, with failure and mortality rates of 3.9% and 2.4%, respectively. Dehiscence and re-stenosis have an incidence of 5–6%.[1] Intravenous anaesthetic techniques during resection are routine so that most management decisions concern how the nature and site of the lesion relate to safeguarding the airway on induction of anaesthesia, during resection, reconstruction and after operation.[6]

By fixing a MLT tube to a shortened LMA, we ensured that the tip did not move from its critical position once the tracheal dehiscence had occurred. The inflated cuff of the LMA offered some protection of the larynx and upper trachea from aspiration of secretions from the oesophagus and the oro-pharynx. Some suctioning of the larynx was possible through the LMA with a small catheter. In addition, the LMA served as a conduit for expiration and reduced the risk of increased expiratory resistance and accidental PEEP developing from the HFPPV.

The morbidity of tracheal resection is significant and includes the potential for life-threatening dehiscence. Although the fundamental problem is the poor vascularity and healing properties of tracheal and bronchial anastomoses, it is likely that the presence of an inflated tracheal cuff close to the anastomosis may contribute. If such is the case, we suggest that the use of a LMA to support a small uncuffed tube for the delivery of HFPPV may reduce the trauma and in some measure reduce the incidence of one of the fearsome complications of tracheal resection.

References

1 Grillo HC, Donahue DM. Postintubation tracheal stenosis. *Chest Surgery Clinics of North America* 1996; **6/4**: 725–31

2 Paes ML, Conacher ID, Snellgrove TR. A ventilator for carbon dioxide laser bronchoscopy. *Br J Anaesth* 1986; **58**: 663–9

3 Nopren M, Schlesser M, Meysmann M, D'Haese J, Peche R, Vincken W. Bronchoscopic balloon dilatation in the combined management of postintubation stenosis of the trachea in adults. *Chest* 1997; **112**: 1136–40

4 Nesbitt JC, Carrasco H. Expandable stents. *Chest Surgery Clinics of North America* 1996; **6/2**: 305–28

5 Conacher ID, Paes ML, McMahon CC. Anesthetic management of laser surgery for central airway obstruction. *J Cardiothor Vasc Anesth* 1998; **12**: 1–5

6 Pinsonneault C, Fortier J, Donati F Tracheal resection and reconstruction. *Canad J Anesth* 1999; **46**: 439–55

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Microalbuminuria following anaphylaxis with general anaesthesia

P. R. Wood[1]*, P. Gosling[1] and M. C. Cook[2]

[1]University Hospital Birmingham NHS Trust, Selly Oak Hospital, Birmingham B29 6JD, UK.
[2]The University of Birmingham Medical School, Birmingham, UK
**Corresponding author*

Microalbuminuria is increasingly recognized as a marker of pathologies that cause acute systemic capillary leak. We report a case of an anaphylactic reaction to general anaesthesia involving cardiac arrest. In this case the urinary excretion of albumin following resuscitation suggests that severe anaphylaxis is another condition for which microalbuminuria is a sensitive monitor.

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Microalbuminuria secondary to systemic capillary leak is increasingly recognized in association with a number of acute medical and surgical conditions. We present a case of drug-induced anaphylaxis in which serial measurement of urinary albumin was made during resuscitation and subsequent intensive care. The potential role of microalbuminuria as a sensitive monitor of the systemic inflammatory response is discussed.

Case report

A 14-yr-old male, weighing 62 kg presented for surgery to release axillary contractures. Fourteen months previously the patient had sustained a 58% body surface area electrical burn and prior to this procedure he had already received 15 general anaesthetics, involving the uneventful administration of atracurium and morphine (both 11 times) and ondansetron (four times). Physically he was left with a

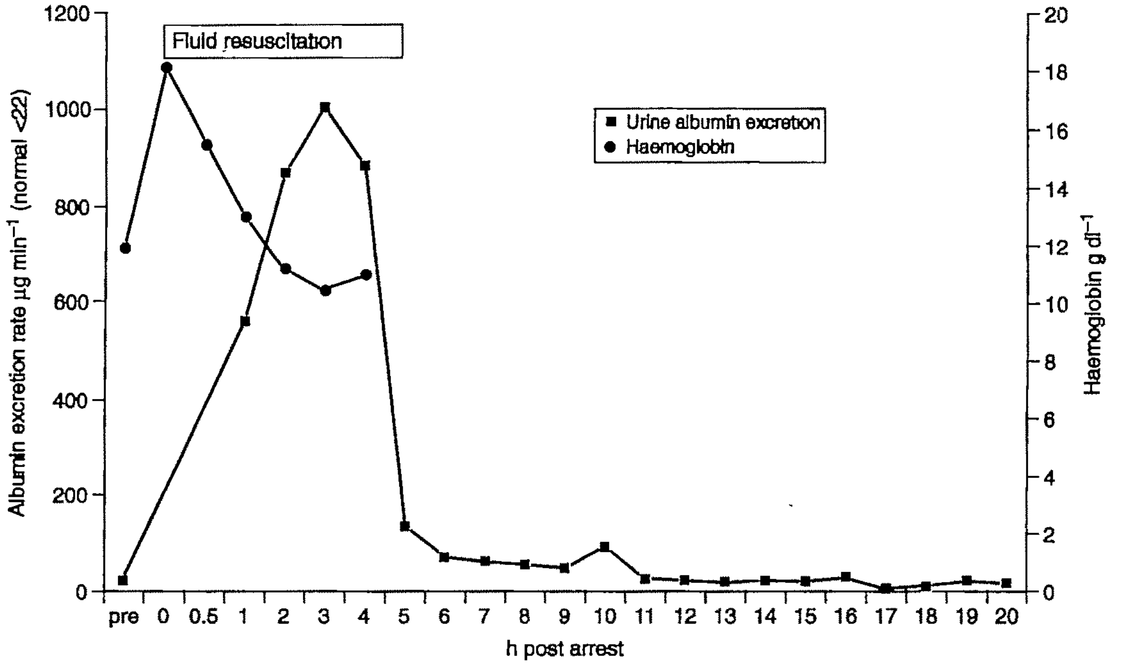

Fig 1 Urine albumin excretion and haemoglobin following anaphylaxis and resuscitation. The fluid resuscitation block indicates volume loading with crystalloid and colloid in addition to normal maintenance requirements.

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below knee amputation and upper body contractures, but was otherwise well. On admission to hospital, physical examination of his airway and cardio-respiratory system were unremarkable. Arterial pressure and heart rate (sinus rhythm) were both within normal limits. Preoperative serum electrolyte and urea concentrations were normal (potassium 4.1 mmol litre^{-1}) and haemoglobin concentration was 13.8 g dl^{-1} (haematocrit 41%). He was not taking any medication. Unpremedicated induction of anaesthesia occurred with up to 8% servoflurane and 40% nitrous oxide in oxygen, during which oxygen saturation and ECG were monitored. After loss of consciousness an i.v. cannula was inserted and ondansetron 4 mg, morphine 3 mg and atracurium 30 mg given in sequence and flushed with normal saline. An initial brief period of resistance to hand ventilation with a bag and mask was immediately followed by rapid arterial oxygen desaturation, from 97% to 75% with an associated sinus bradycardia of 50 beat min^{-1}. The trachea was intubated immediately and hand ventilation continued with 100% oxygen, while glycopyrrolate 0.2 mg was administered i.v. In spite of these measures the patient became pulseless, and external chest compression was started.

After a 20-min period of resuscitation involving the administration of 2 litres of normal saline, epinephrine 3 mg (three bolus injections of 1 mg) and atropine 3.6 mg (0.6 mg + one 3 mg bolus), a sinus tachycardia (160 beat min^{-1}) rhythm was restored with an arterial pressure of 100/60 mm Hg. Arterial blood-gas analysis immediately post-resuscitation revealed H^+ 73.8 nmol litre^{-1}, Pa_{CO_2} 5.14 kPa and Pa_{O_2} 62.3 kPa with a base excess of −16 mmol litre^{-1}. The haemoglobin had risen to 18.1 g dl^{-1} (haematocrit 53%).

The patient was sedated with propofol and transferred to the intensive care unit (ITU) for mechanical ventilation and stabilization of his condition. On admission to ITU, arterial blood-gas analysis revealed a metabolic acidosis, H^+ 67.3 nmol litre^{-1}, Pa_{CO_2} 5.19 kPa and Pa_{O_2} 65.24 kPa with a base excess of −14.5 mmol litre^{-1} and a chest x-ray showed evidence of pulmonary oedema but was otherwise normal. At this time the patient was noted to have a pink rash, and serial blood and urine samples were taken to investigate the cause of his collapse.

Serum tryptase activities (reference range 4–14 μg litre^{-1}) immediately after the cardiac arrest, and 3 and 24 h later were >200, 151 and 39.5 μg litre^{-1}, respectively. Hourly capillary permeability was assessed by urine albumin excretion rates (reference range <9.1 μg min^{-1}), which 1 h post-arrest, and after 3 and 15 h, respectively were 563, 1006 and 6.1 μg min^{-1} (Fig. 1). The immediate post-resuscitation haemoglobin of 18.1 g dl^{-1} (a finding consistent with an initial shift of protein and water into the interstitial space) had fallen to 11.0 g dl^{-1} 5 h later after further fluid resuscitation (Fig. 1). The patient's lungs were ventilated for 3 days during which the only biochemical abnormality was a slowly resolving metabolic acidosis. All sedation was then discontinued until he could be extubated safely. His Glasgow Coma Score was 9 on discharge from the ITU, and a computerized tomographic scan of his brain performed 6 days post-arrest was reported as normal although electroencephalograms performed at 6 and 16 days post-incident demonstrated changes consistent with global cerebral hypoxia.

One month after discharge from ITU *in vivo* allergy tests to skin prick and intradermal injection were performed to identify sensitivity to a range of other neuromuscular blockers. The patient was subsequently issued with a medical alert bracelet and a 'statement of clinical events', including a list of the drugs involved in this incident and the results of the *in vivo* tests. He was discharged to neurological follow up and at the time of writing has made a substantial neurological recovery.

Discussion

This patient's clinical presentation, response to treatment and the subsequent serum tryptase analysis strongly support a diagnosis of anaphylaxis from a type 1 hypersensitivity reaction. The tryptase levels documented in this patient are rarely seen without anaphylaxis,[1] and furthermore the time course of the decline in the serum tryptase is also consistent with systemic mast cell degranulation at the time of cardiovascular collapse.[2]

Mast cell degranulation does occur as a direct pharmacological action of narcotics, especially morphine. However, in such cases the serum tryptase is only moderately elevated. Type I hypersensitivity to morphine may also occur and the possibility of this 'dual' histamine release makes the interpretation of subsequent intradermal testing problematic. Hypersensitivity to ondansetron is relatively rare,[3] and to our knowledge there are still no reports of suspected anaphylaxis to inhalation agents.

Anaphylaxis from neuromuscular blocking drugs is responsible for the majority of anaesthesia-related reactions,[4] and cross-sensitivity between neuromuscular blocking drugs occurs in up to 60% of patients[5] so that determination of safe drugs for future anaesthesia is a priority in the investigation of the patient. The subsequent investigation of our patient followed published guidelines[6] in an effort to determine safe alternatives to atracurium.

The systemic inflammatory response syndrome (SIRS) is recognized as a non-specific and generalized response to a variety of traumatic and infective pathologies. Studies in trauma and burn patients have demonstrated that the severity of injury and subsequent development of SIRS correlates positively with an increase in urine albumin excretion (microalbuminuria),[7 8] detectable only by sensitive immunoassay. Microalbuminuria is defined as a spot urinary albumin concentration of 30–200 mg litre^{-1}, or alternatively as an excretion rate greater than 9.1 μg min^{-1}.[9] It is a feature of such diverse conditions as elective aortic aneurysm surgery, pancreatitis, bacterial meningitis and myocardial infarction.[10] The underlying mechanism is loss of capillary membrane integrity which permits generalized protein leak.[11] What is not certain is the extent to which the degree of albuminuria may be predictive of the subsequent clinical course in different conditions.[12]

Urine albumin excretion has been measured in 20 previously healthy individuals following bee or wasp stings.[13] Abnormal values were recorded in three patients, whereas normal values were obtained in three other patients who were hospitalized with hypotension, respiratory problems and generalized urticaria, although the severity of their anaphylaxis is not stated. Urine was collected the morning after admission so it is possible that post-anaphylaxis microalbuminuria had resolved.

In contrast, our patient was monitored continuously for the first 20 h following anaphylaxis, during the first 5 h of which he developed clinical albuminuria (Fig. 1).

The albumin excretion we measured mirrored the elevation and decline in serum tryptase activity during the period of maximum capillary leak, and we believe that anaphylaxis may be another pathology in which microalbuminuria may serve as a non-specific but sensitive marker of the acute inflammatory response. Microalbuminuria cannot, in isolation, confirm a diagnosis of anaphylaxis but it may have prognostic value. Confirmation of this possibility in other cases of anaphylaxis would be dependent on albumin excretion being measured as near as possible from the time of onset, up to 12 h later.[2]

References

1 Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast cell activation in systemic anaphylaxis and mastocytosis. *N Eng J Med* 1987; **316**: 1622–6

2 Schwartz LB, Yunginger JW, Miller J, Bokhari R, Dull D. Time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest* 1989; **83**: 1551–5

3 Chen M, Tanner A, Gallo-Torres H. Anaphylactoid-anaphylactic reactions associated with ondansetron. *Ann Intern Med* 1993; **119**: 862

4 Pepys J, Pepys EO, Baldo BA, Whitwam JG. Anaphylactic/anaphylactoid reactions to anaesthetic and associated agents. *Anaesthesia* 1994; **49**: 470–5

5 Fisher M, Munro I. Life threatening anaphylactoid reactions to muscle relaxants. *Anesth Analg* 1983; **62**: 559–64

6 Association of Anaesthetists of Great Britain and Ireland and British Society of Allergy and Clinical Immunology. *Suspected Anaphylactic Reactions Associated with Anaesthesia* (revised edition), 1995

7 Gosling P, Sutcliffe A. Proteinuria following trauma *Ann Clin Biochem* 1986; **23**: 681–5

8 Shakespeare PG, Coombes EJ, Hambleton J. Proteinuria after burn injury. *Ann Clin Biochem* 1981; **18**: 353–60

9 Watts GF, Morris RW, Khan K, Polak A. Urinary albumin excretion in healthy adult subjects: reference values and some factors affecting their interpretation. *Clinica Chimica Acta* 1988; **172**: 191–8

10 Gosling P. Microalbuminuria: a marker of systemic disease. *Br J Hosp Med* 1995; **54**: 285–90

11 Jensen JS, Borch-Johnsen K, Jensen G, Feldt-Rasmussen B. Microalbuminuria reflects a generalised transvascular albumin leakiness in clinically healthy subjects. *Clin Sci* 1995; **88**: 629–33

12 Evans G, Greaves I Microalbuminuria as predictor of outcome. *Br Med J* 1999, **318**: 207–8

13 Elming H, Solling K. Urine protein excretion after Hymenoptera sting. *Scand J Urol Nephrol* 1994; **28**: 13–5

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BJA

EQUIPMENT

Laboratory assessment of the Bird T-Bird VS ventilator performance using a model lung

L. S. S. Wong[1]* and N. M. McGuire[2]

[1]Nuffield Department of Anaesthetics, Level 1, JR2, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK. [2]Tactical Medical Wing, Royal Air Force Lyneham, Chippenham SN15 4PZ, UK

*Corresponding author

We assessed the Bird T-Bird VS ventilator using a model lung constructed to standard 10651–1 of the International Standards Organization. We used different combinations of lung compliance and airway resistance to simulate normal and diseased adult and paediatric lungs. Different preset tidal volumes at various respiratory rates were delivered to the model lung and compared with the actual measured tidal volumes. The results showed that the delivered tidal volumes were within the manufacturer's specification of ±10% of the preset tidal volumes in normal adult and paediatric combinations of lung compliance and airway resistance. The ventilator can be powered by mains electricity supply or battery and requires only optional compressed oxygen. The ventilator is suitable for the provision of advanced ventilatory support during prolonged patient transfer.

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In the UK, the number of inter-hospital patient transfers has increased in recent years and is likely to continue increasing.[1] One of the major problems with the transfer of critically ill patients is the provision of ventilatory support. This is a particular problem in aeromedical transfers, which may sometimes exceed 24 h. Carrying large quantities of oxygen by air is difficult and hazardous, so the search for a high-specification ventilator with low oxygen consumption is necessary.

A number of ventilators have been assessed by the Royal Air Force for this purpose. One such ventilator is the Bird T-Bird VS ventilator (Bird Products Corp., CA, USA). We assessed it in a laboratory study in which a model lung was adjusted to simulate normal and diseased adult and paediatric lungs. A volume performance test[2–5] and a waveform test, which most studies have omitted, were used to evaluate the ventilator performance.

Materials and methods

Ventilator

The Bird T-Bird VS ventilator is designed to provide positive-pressure ventilation for patients over 10 kg who require advanced ventilatory support. The ventilation modes and breath types provided by the ventilator are shown in Table 1.

Pressurized air is supplied by an electrically powered drag turbine in which the speed of the outlet gas is controlled by the gas drag action caused by the rotating turbine blades.[6] Low-pressure (35 mbar maximum) oxygen can be added at the oxygen inlet upstream of the turbine to adjust the inspired oxygen concentration. A microcomputer controller monitors the output pressure and controls the turbine speed to generate the required breath settings and modes of ventilation.

The ventilator can be powered by mains electricity or battery. The fully charged internal rechargeable battery is capable of providing 25 min of continuous power, and a replaceable external battery provides up to 3.5 h depending on the load applied.

The breathing systems used for the adult and paediatric settings were Intersurgical Model 2019–045 22 mm Adult Breathing System and Intersurgical Model 4500 15 mm Paediatric Breathing System (Intersurgical Ltd, Wokingham, Berks, UK) with compliance 1.3 and 0.6 ml cmH_2O^{-1} respectively. Neither breathing circuit contained water-trap, bacterial filter or humidifier.

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Table 1 Ventilation modes and breath types supported by the Bird T-Bird VS ventilator. *Apnoea back up ventilation is provided CPAP = continuous positive airway pressure, SIMV = synchronized intermittent mandatory ventilation

Breath type	**Ventilation mode**			
	Control	**Assist/Control***	**SIMV**	**CPAP**
Volume control	Yes	Yes	Yes	No
Pressure support	No	No	Yes	Yes
Spontaneous	No	No	Yes	Yes
Manual	Yes	Yes	Yes	Yes
Sigh	Yes	Yes	Yes	Yes

Table 2 Specifications of the lung model compliance and resistance

Compliance ($ml\ cmH_2O^{-1}$) ±5% tolerance	**Chamber volume (litre)**	**Resistance ($cmH_2O\ litre^{-1}\ s$)**	**Flow range ($litre\ s^{-1}$) ±20% tolerance**
50	51.6	5	0–2.0
20	20.6	20	0–1.0
10	10.3	50	0–0.5
3	3.09	200	0–0.1
1	1.03	500	0–0.005

Model lung

A model lung constructed to the International Standards Organization (ISO) standard *Lung ventilators for medical use–Part 1: Requirements* (ISO 10651–1:1993) was used to simulate the respiratory compliance and airway resistance of normal and diseased adults and children.[7] It consisted of a series of rigid copper isothermal compliance chambers and linear resistance modules (Table 2).[8–11] Previous studies have shown that the ISO model lung is preferable to the more common commercially available test lungs based on spring and bellows constructions for the purpose of assessing the performance of ventilators.[7 8 11] The normal adult and paediatric lung compliance values were 50 and 20 ml cmH_2O^{-1} respectively, and the normal adult and paediatric airway resistance values were 5 and 20 cmH_2O $litre^{-1}$ s respectively. To simulate reduced adult and paediatric lung compliance, values of 20 and 10 ml cmH_2O^{-1} respectively were used, and for constricted adult and paediatric airways resistances of 20 and 50 cmH_2O $litre^{-1}$ s respectively were used.

Measurement and calibration

A block diagram of the apparatus is shown in Figure 1. Gas flow was measured using a Fleisch pneumotachograph (input range, ±125 litre min^{-1}) (Hamilton Medical, Reno, NV, USA) and a Validyne MP45-1 differential pressure flow transducer (input range, ±2.0 cmH_2O) connected to a Validyne MC1-3 flow amplifier (Validyne Engineering Corp., Northridge, CA, USA). Airway and alveolar pressures were measured using Statham PM131T strain gauge pressure transducers (input range, ±175 cmH_2O) (Gulton Statham Transducer Inc., Costa Mesa, CA, USA) connected to Lectromed strain gauge amplifiers (Ormed Engineering Ltd, Welwyn Garden City, Herts, UK). The airway pressure transducer was placed at a sampling port in series and upstream of the pneumotachograph and the alveolar pressure transducer was placed at the sampling port at the compliance chamber housing. Two-point calibrations were used to calibrate the flow and pressure transducers. Reference values were provided by a Timeter RT-200 calibration analyser (Timeter Instrument Ltd, St Louis, MO, USA).

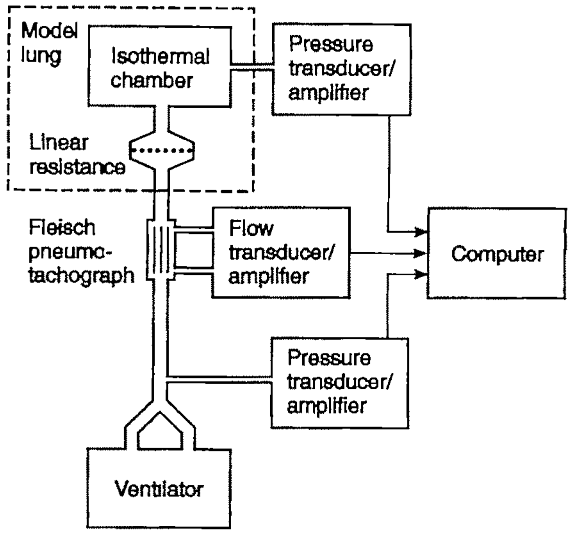
Model lung
Isothermal chamber
Pressure transducer/ amplifier
Linear resistance
Fleisch pneumo-tachograph
Flow transducer/ amplifier
Computer
Pressure transducer/ amplifier
Ventilator

Fig 1 Block diagram of the apparatus.

Data acquisition and analysis

The gas flow, airway pressure and alveolar pressure signals were digitized using a National Instrument AT-MIO16 data acquisition card (National Instrument Corp., Austin, TX, USA) in an IBM-compatible personal computer. The signals were displayed continuously and stored using the data acquisition/analysis software developed in the department. Data for each ventilator setting were recorded at a sampling rate of 500 Hz for at least five respiratory cycles. Data were analysed off-line. The flow signal was integrated to give the volume signal. Inspired tidal volume was determined by integrating the flow signal during inspiration. The inspired tidal volume values presented are the mean and standard deviation of five consecutive respiratory cycles.

Waveform test

The ventilator was set to deliver the combinations of tidal volume, respiratory rate, lung compliance and airway resistance shown in Table 3. Without changing the ventilator settings, the next compliance–resistance combination was then substituted in turn. Comparisons of the waveforms of flow, volume, and airway and alveolar pressure with changing lung characteristics determine the conditions under which the shapes of the waveforms begin to change and if the ventilator performance is likely to deteriorate. The flow waveform can affect gas distribution in the lungs.[12–14] Leakage through delivery tubing, mechanical valves and other pneumatic design faults also can be revealed by the waveform test.

Table 3 Lung compliance, airway resistance, tidal volume and respiratory rate combinations for the waveform test

Test sequence	Compliance (ml cmH_2O^{-1})	Resistance (cmH_2O litre^{-1} s)	Tidal volume (ml)	Respiratory rate (b.p.m.)
Adult settings				
1	50	5	600	12
2	50	20	600	12
3	20	5	600	12
4	20	20	600	12
Paediatric settings				
1	20	20	300	20
2	20	50	300	20
3	10	20	300	20
4	10	50	300	20

Table 4 Lung compliance, airway resistance, tidal volume and respiratory rate combinations for the volume performance test

Compliance (ml cmH_2O^{-1})	Resistance (cmH_2O litre^{-1} s)	Ventilator settings: tidal volume (V_T; ml) and respiratory rate (RR; b.p.m.)
Adult settings		
50	5	V_T = 200 at RR = 20 and 30,
50	20	V_T = 400, 600, 800 and 1000 at RR = 10 and 12
20	5	
20	20	
Paediatric settings		
20	20	V_T = 100 at RR = 30 and 40;
20	50	V_T = 200 at RR = 20, 30 and 40;
10	20	V_T = 300 at RR = 15, 20, 30 and 40
10	50	

Volume performance test

This test finds the accuracy of the tidal volume delivered over a wide range of respiratory frequencies at a fixed inspiration:expiration (I:E) ratio of 1:2. The choices of lung compliance, airway resistance, tidal volume and respiratory rate combinations for the test were clinically realistic instead of the exhaustive, but sometimes clinically unrealistic, settings used in previous studies.[7 11] They are shown in Table 4. The accuracy of the tidal volume delivered by the ventilator with different lung characteristics and respiratory rates is an important indicator of the ventilator performance.

Results

Waveform test

The waveforms of the flow, volume, airway pressure and alveolar pressure for adult and paediatric settings are shown in Figure 2. For adult settings (Fig. 2A), except for a slight decrease in the last compliance–resistance combination, i.e. compliance = 20 ml cmH_2O^{-1}, resistance = 20 cmH_2O litre^{-1} s (C20, R20), the peak flow remained the same. For the paediatric settings (Fig. 2B), the peak flow decreased slightly with decreasing compliance and increasing resistance. The overall shapes of the decelerating flow waveforms at both adult and paediatric settings remained consistent. There was no change in the inspiratory and expiratory times with decreasing compliance and increasing resistance for either adult or paediatric settings. At paediatric settings, there were high-frequency oscillations on the diaphragm of the ventilator expiratory valve at the onset of expiration when the ventilator was set to deliver to a lung compliance below or equal to 20 ml cmH_2O^{-1} (Fig. 2B). The oscillations became more vigorous with decreasing compliance and increasing resistance.

The volume waveforms in Figure 2 show that the tidal volume delivered changed only slightly with decreasing compliance and increasing resistance. There was a decrease (from 313 to 295 ml, equivalent to 0.36 litre min^{-1} at 20 b.p.m.) in the volume delivered with decreasing compliance from 20 to 10 ml cmH_2O^{-1} at paediatric settings and a decrease (from 597 to 522 ml, equivalent to 0.9 litre min^{-1} at 12 b.p.m.) in volume delivered with increasing resistance at 20 ml cmH_2O^{-1} lung compliance at adult settings. All the volume waveforms at the paediatric settings showed that the test lung was not completely emptied at the end of expiration, which was less evident with a small compliance and more evident with greater resistance. The peak airway pressure increased with decreasing compliance and increasing resistance.

The alveolar pressure waveforms in Figure 2 indicated that there was no standing pressure developed in the lung at end-expiration during use with adult settings, but positive pressures were developed in the lung at end-expiration when paediatric settings were used, and the magnitude was greater with the greater airway resistance.

Volume performance test

The percentage errors of the tidal volume delivered at adult and paediatric settings at different compliance–resistance combinations are shown in Figures 3 and 4 respectively.

In Figure 3A and B, at normal adult lung compliance (50 ml cmH_2O^{-1}) with normal (5 cmH_2O litre^{-1} s) and increased (20 cmH_2O litre^{-1} s) airway resistance, the average tidal volumes measured at various respiratory rates were within the manufacturer's specification, i.e. ±10% of the preset tidal volume, except for the preset tidal volume of 800 ml at 10 b.p.m. and 1000 ml at 10 b.p.m. at C50, R5. In Figure 3C and D, at reduced adult lung compliance (i.e. 20 ml cmH_2O^{-1}), the ventilator performance began to deteriorate when the tidal volume was set above 600 ml at both 10 and 12 b.p.m. Furthermore, the ventilator consistently underdelivered the preset tidal volumes. The percentage error of the average tidal volume delivered increased with increasing tidal volume setting and with increasing respiratory rate. The worst average error was −18.0% (SD = 0.45%) at 1000 ml preset tidal volume at 12 b.p.m. at C20, R20.

In Figure 4A and B, at normal paediatric lung compliance (20 ml cmH_2O^{-1}) with normal (20 cmH_2O litre^{-1} s) and increased (50 cmH_2O litre^{-1} s) airway resistance, the average tidal volumes measured at various ventilation settings were within the manufacturer's specification except for the

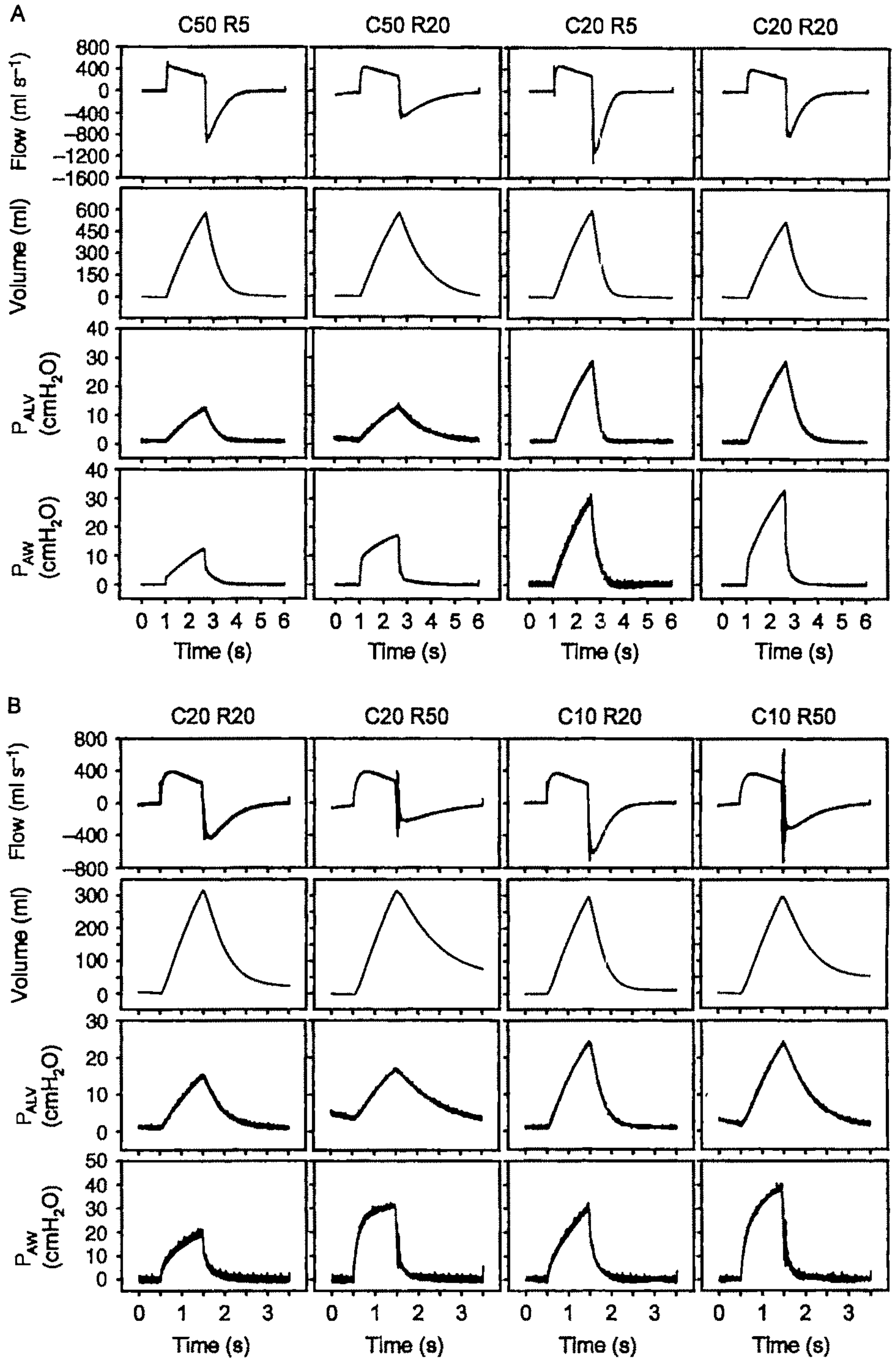

Fig 2 Waveform test results at (A) adult and (B) paediatric settings. P_{ALV} = alveolar pressure in cmH_2O; P_{AW} = airway pressure in cmH_2O; C# = lung compliance in # ml cmH_2O^{-1}; R#* = airway resistance in #* cmH_2O litre^{-1} s.

preset tidal volume of 300 ml at 40 b.p.m. at C20, R20, 200 ml at 20 b.p.m. and 300 ml at 30 and 40 b.p.m. at C20, R50. In Figure 4C and D, at small paediatric lung compliance (i.e. 10 ml cmH_2O^{-1}) with the same normal and increased airway resistances as those mentioned above, the ventilator performance was within the manufacturer's specification except for the preset tidal volume of 300 ml at 30 and 40 b.p.m. at C10, R20, 200 ml at 40 b.p.m. and 300 ml at 30 and 40 b.p.m. at C10, R50.

Discussion

From the paediatric waveform test results (Fig. 2B), the persistent flow during expiration is a result of the long time

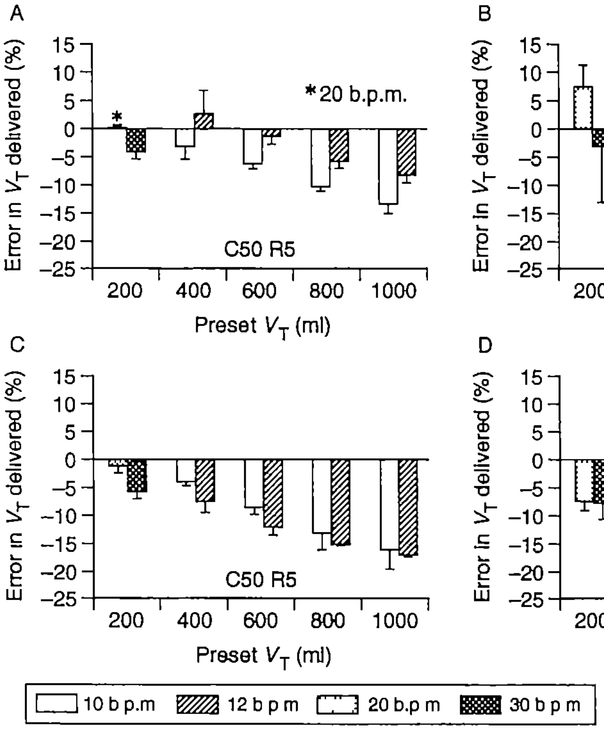

Fig 3 Volume performance test results over five consecutive breaths (mean and SD) at adult settings. V_T = inspired tidal volume; C# = lung compliance in # ml cmH$_2$O^{-1}; R#* = airway resistance in #* cmH$_2$O litre^{-1} s.

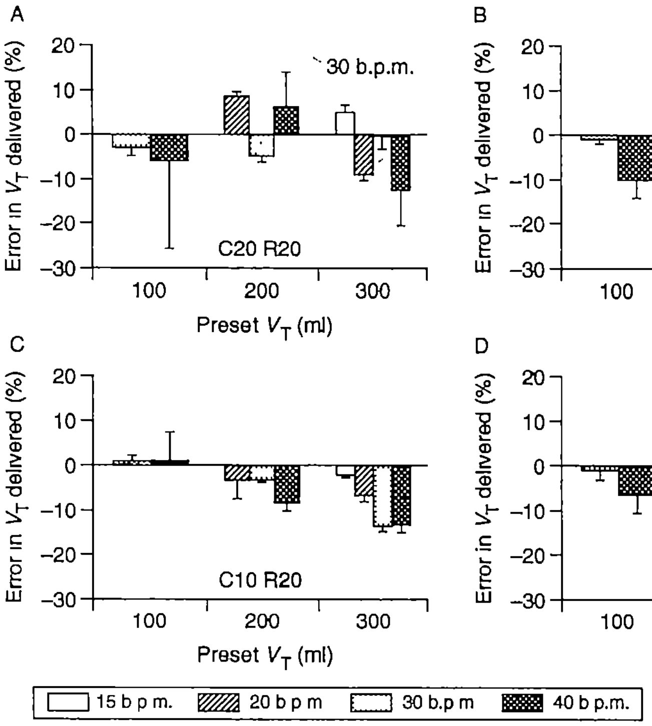

Fig 4 Volume performance test results over five consecutive breaths (mean and SD) at paediatric settings. V_T = inspired tidal volume; C# = lung compliance in # ml cmH$_2$O^{-1}; R#* = airway resistance in #* cmH$_2$O litre^{-1} s.

constant (i.e. the product of lung compliance and airway resistance) of the compliance–resistance combination prolonging expiratory flow to such an extent that the model lung does not empty fully before the onset of the next inspiration. Because of the greater time constant, the gas remaining in the test lung at the end of expiration increased with increasing resistance. Consequently, as observed from the alveolar pressure waveforms, positive standing pressures were developed in the model lung. In human physiology, this is analogous to auto-positive end-expiratory pressure, which occurs when insufficient time elapses between inflation cycles to establish the equilibrium position of the respiratory system.[15 16] Alveolar pressure remains continuously positive through both phases of the ventilation cycle. Airflow does not cease before the end of expiration. The lung volume and alveolar pressure at the end of expiration increase with each subsequent ventilatory cycle. The lung volume will increase to the point at which the lung compliance becomes less and increases tissue recoil. This increases the driving force for expiratory flow and tethers open obstructed airways, lowering airflow resistance.[17] Within several cycles, the lung volume will reach a value at which the entire delivered tidal volume can be exhaled; this is associated with increased end-expiratory alveolar pressure.

The ventilator expiratory valve assembly consists of a high-energy permanent magnet core. When electric current is applied to the suspended magnetic coil, the core is drawn into the magnetic field that is generated and mechanically forces the expiratory valve diaphragm to close the expiratory path during inspiration. During expiration, current to the coil is stopped and the expiratory valve diaphragm is returned to its normally open position. The paediatric waveform test results (Fig. 2B) show oscillations on the expiratory valve diaphragm at the onset of expiration with settings of low lung compliance and high airway resistance. The oscillations became more vigorous with decreasing compliance and increasing resistance. Since the respired volume signal is derived by integrating the flow signal, the high-frequency oscillations at the onset of expiration are not related exactly to gas flow. If the integrated signal is in error, the difference between inspired and expired gas volume cannot be used to assess gas trapping. This is better done by inspection of the alveolar pressure signal. If gas trapping is present, the end-expiratory pressure will be positive. This can be seen from the alveolar pressure waveforms during paediatric tests (Fig. 2B). The end-expired alveolar pressures were approximately 3.5 and 2.1 cmH_2O at C20, R50 and C10, R50 respectively, indicating incomplete emptying of the lung. The adult waveform test results (Fig. 2A) showed that at a short time constant and adequately long expiratory time, the model lung emptied completely at the end of expiration.

At very low tidal volume settings (e.g. 50 ml), with the minimum peak flow of the ventilator limited to 10 litre min^{-1}, the desired volume cannot be delivered without increasing the I:E ratio. From the volume performance test results shown in Figures 3 and 4, the mean error of the tidal volumes delivered was within the manufacturer's specification of ±10% of the preset tidal volumes when delivered to normal adult and paediatric lungs. The tidal volumes delivered at both adult and paediatric settings were consistently less than the preset values when delivered to stiff lungs (i.e. low lung compliance) or lungs with high airway resistance. The reason for this is related to the breathing system compliance, i.e. gas compression in the ventilator and conducting tubing.[11] Results in Figures 3 and 4 show that the tidal volume lost by gas compression in the breathing system is more pronounced at paediatric settings, i.e. with small tidal volumes and high airway pressures. Such underdelivery of tidal volume against a large load is common to turbine-driven ventilators[18] and the mean error observed is not excessive. The underdelivery of tidal volume can be easily identified and compensated for when verification of the adequacy of ventilation, e.g. independent exhaled volume and arterial blood gas monitoring, is carried out, which we strongly recommend to check the ventilator performance.

In Figure 2, the inspiratory flow pattern at adult and paediatric settings is decelerating, which may provide better distribution of ventilation.[12–14] At the same ventilator settings, the peak flow and the inspiratory duration remained almost constant with the changes of compliance–resistance combinations except for the worst case of peak flow decrease at paediatric settings, i.e. from 413 to 381 ml s^{-1} at C20, R50 to C10, R20 respectively, which was clinically insignificant. This implied that adjustment of the ventilator settings was not required if sudden changes in lung characteristics occurred.

The ventilator performed within its specification at various compliance–resistance combinations of the model lung, i.e. simulated normal and diseased lungs of adults and children. Because of its portability, adequate monitoring facilities, long battery life and altitude compensation, the Bird T-Bird VS ventilator is suitable for advanced ventilatory support during prolonged patient transfer.

The altitude compensation feature, which makes the ventilator suitable for aeromedical transport, is normally set at 147 m and is adjustable within the range of −305 to 3048 m. However, the ventilator performance at altitude is yet to be evaluated.

Acknowledgement

We gratefully acknowledge the editorial help of Dr J. D. Young at the Nuffield Department of Anaesthetics, University of Oxford, Oxford, UK.

References

1 Oakley PA. The need for standards for inter-hospital transfer. *Anaesthesia* 1994; **49**: 565–6

2 Rothschiller JL, Uejima T, Dsida RM, Cote CJ. Evaluation of a new operating room ventilator with volume-controlled ventilation: the Ohmeda 7900. *Anesth Analg* 1999; **81**: 39–42

3 McCluskey A, Gwinnutt CL. Evaluation of the Pneupac Ventipac portable ventilator: comparison of performance in a mechanical lung and anaesthetized patients. *Br J Anaesth* 1995; **75**: 645–50

4 Beydon L, Liu N, Hassapopoulos J, *et al.* Test of 20 similar intensive care ventilators in daily use conditions–evaluation of accuracy and performances. *Intensive Care Med* 1992; **18**: 32–7

5 Johnson A, Bengtsson M. Comparison of anaesthesia ventilators using a lung model. *Acta Anaesthesiol Scand* 1990; **34**: 222–6

6 Cohen H, Rogers GFC, Saravanamuttoo HIH. *Gas Turbine Theory.* London: Addison-Wesley Longman, 1996: 103–5

7 Chakrabarti MK, Sykes MK. Evaluation of the lung ventilator performance analyser. *Anaesthesia* 1976; **31**: 521–8

8 Hill DW, Moore V. The action of adiabatic effects on the compliance of an artificial thorax. *Br J Anaesth* 1965; **37**: 19–22

9 Burton GW, Fox DER. An airway resistance for use in an artificial lung. *Br J Anaesth* 1972; **44**: 1253–62

10 Saklad M, Weyerhaeuser R. The construction of linear resistances for the testing of ventilators. *Anaesthesiology* 1980; **52**: 71–3

11 Loh L, Sykes MK, Chakrabarti MK. The assessment of ventilator performance. *Br J Anaesth* 1978; **50**: 63–71

12 Hedenstierna G, Johansson H Different flow patterns and their effect on gas distribution in a lung model study. *Acta Anaesthesiol Scand* 1973; **17**: 190–6

13 Jansson L, Jonson B. A theoretical study on flow patterns of ventilators. *Scand J Respir Dis* 1972; **53**: 237–46

14 Lyager S. Influence of flow pattern on the distribution of respiratory air during intermittent positive-pressure ventilation *Acta Anaesthesiol Scand* 1968; **12**: 191–211

15 Pepe PE, Marini JJ Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction: the auto-PEEP effect. *Am Rev Respir Dis* 1982; **126**: 166–70

16 Rossi A, Gottfried SB, Zocchi L, *et al.* Measurement of static compliance of the total respiratory system in patients with acute respiratory failure during mechanical ventilation. The effect of 'intrinsic PEEP'. *Am Rev Respir Dis* 1985; **131**: 672–7

17 Murray JF. *The Normal Lung*. Philadelphia: W B. Saunders Co., 1976; 98–104

18 Watt JWH, Fraser MH. The effect of insufflation leaks upon ventilation–a quantified comparison of ventilators. *Anaesthesia* 1994; **49**: 320–3

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BJA

COMMENTARY

Recommendations for uniform reporting of data following major trauma–the Utstein style. An International Trauma Anaesthesia and Critical Care Society (ITACCS) initiative[1]

W. F. Dick (Germany)* †, P. J. F. Baskett (UK)†, C. Grande (USA), H. Delooz (Belgium), W. Kloeck (South Africa), C. Lackner (Germany), M. Lipp (Germany), W. Mauritz (Austria), M. Nerlich (Germany), J. Nicholl (UK), J. Nolan, (UK), P. Oakley (UK), M. Parr (UK/Australia), A. Seekamp (Germany), E. Soreide (Norway), P. A. Steen (Norway), Luc van Camp (Belgium), B. Wolcke (Germany) and D. Yates (UK)

**Corresponding author: Klinik für Anaesthesiologie, Klinikum der Johannes Gutenber Universität, Langenbeckstrasse 1, D-55131 Mainz, Germany*

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Consensus statement

Basic and advanced care of trauma patients has always been an important aspect of prehospital and immediate in-hospital emergency medicine, involving a broad spectrum of disciplines, specialties and skills. This complex background has, however, hindered the development of a uniform pattern of criteria and definitions with the consequence that differing systems or protocols of care cannot be readily evaluated or compared with acceptable validity.

Guided by a previous consensus on 'Uniform reporting of data following cardiac arrest–the Utstein style',[2] an international working group of The International Trauma Anaesthetic and Critical Care Society (ITACCS) has drafted a similar document on major trauma.

The reporting system for out- and in-hospital care is based on the following considerations.

- It should permit the compilation of data and statistics on major trauma care, facilitating and validating the independent or comparative audit of performance and quality of care.
- It should permit intra- and intersystem evaluation to improve the quality of delivered care and identification of the relative benefits of different systems and innovative initiatives.
- It should facilitate studies setting out to improve the epidemiological understanding of trauma.

The document includes a glossary of terms used in the pre-hospital and early hospital phases, including definitions, time points and intervals, and uses a scheme for illustrating the different process time clocks (patient, dispatch centre, ambulance and hospital).

Data should be reported as *core data* (i.e. always obtained) and *optional data* (obtained under specific circumstances).

The document highlights the following.

- The development of structured data using object-orientated modelling.
- Terms and definitions for describing different types of trauma.
- The circumstances of the injury, such as: its cause; its severity (pre-hospital basic abbreviated injury score); its mechanism; its demographics.
- System factors, subdivided into:
  (i) Pre-hospital, inter-hospital transfer and trauma centre/receiving factors: the trauma team, its membership and their respective experience; the facilities available during the 24-h period; arrival data at different transit/treatment locations.
  (ii) Patient factors defining physical characteristics such as age, gender, dimensions and the co-morbidity that may be most important for survival. Co-morbidity is graded ordinally from 1=healthy to 4=systemic illness, a constant threat to life.
  (iii) Outcome, i.e. mortality (time, date, location of death, place, confirmation, cause of death and adverse factors) and morbidity, defined as all non-fatal problems leading from impairment to disability, reversible and irreversible.

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†Co-chairmen.

[1] Full details of the Recommendations may be obtained from ITACCS Headquarters, PO Box 4826, Baltimore, MD 21211, USA and from the above address in Mainz, Germany.

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(iv) Ethical issues, placing special emphasis on patient consent to trauma research, on medical futility, DNAR and DNR directives, deliberate self-inflicted harm, care of relatives and advanced directives.

(v) Documentation underlining the need for data collection to be planned, including details such as manual, automatic and electronic data collection, entry of data, and data collection forms.

The document provides the basis for uniform documentation of data after trauma from the scene to the hospital. It may serve as a tool for both quality control (core data) and/or scientific evaluation (core and optional data) and allows intrasystem evaluation as well as intersystem comparison.

References

1 Co-Chairmen: Dick WF, Baskett PJF, Grande C, *et al.* Recommendations for Uniform Reporting of Data Following Major Trauma–the Utstein style. *Trauma Care* 1999; [Suppl. 9] 1–12 and *Resuscitation* 1999: **42**; 81–100

2 Cummins RO, Chamberlain DA, Abramson NS, *et al.* Recommended Guidelines for Uniform Reporting of Data From Out-of-Hospital Cardiac Arrest: the Utstein style. *Circulation* 1991; **84**: 960–75

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Correspondence

Anaesthesia without anaesthetics—a possible mechanism revisited

Editor—Surgical anaesthesia can be induced by a variety of chemically diverse volatile compounds, similar only in that potency is a function of their oil/water partition coefficient (the Meyer–Overton rule), a relationship which, when plotted on a log-log scale, is linear over at least four orders of magnitude. The Meyer–Overton rule led to the proposal that anaesthetics accumulate within the oil-like non-polar phase of lipid bilayers in nerve cell membranes and alter physical properties such as bilayer fluidity and permeability. Although subtle effects have been detected, it has been difficult to argue that this membrane effect can account for the rate of onset and degree of immobility and amnesia that characterizes surgical anaesthesia.[1]

A second mechanism builds on the fact that nerve cell function is regulated by proteinaceous receptor sites on the cell membrane. A variety of water soluble anaesthetics, such as the benzodiazepines, the opioids and barbiturates clearly affect receptors and thereby produce anaesthesia. This evidence led to the proposal that volatile anaesthetics may also act as receptors, and some of the newer mechanisms proposed for their action have arisen from tests of this idea.[2] Recent examples include the effects of xenon on the NMDA receptor,[3] inhibition of luciferase[4] and genetic modification of receptor sites[5–7] (see ref. 8 for a recent comprehensive review of anaesthetic mechanisms). As a result of these observations, a growing consensus suggests that volatile anaesthetics act directly on a variety of proteins related to nerve cell membrane function.

Despite intensive study we still do not fully understand how agents that induce general anaesthesia work. Furthermore, our understanding of the induction of anaesthesia by reductions of body temperature (Fig. 1) and hypoxia is even more limited. For example how can anaesthesia be induced in the complete absence of anaesthetics? Clearly this can have nothing to do with anaesthetic effects on either lipid or protein sites. And it has long been known that consciousness is lost when mammalian body temperature decrease below 32°C.[9] Other examples include loss of consciousness when oxygen partial pressures are decreased (one of the authors being taught, albeit 50 years ago, to deliver nitrous oxide to dental patients until their faces turned blue) and fainting following mutual strangulation by indulgent school children.[10] Are these forms of 'suspended animation' unique, or can they be accommodated by any of the anaesthetic mechanisms that have been proposed? We suggest that it is caused by the potential vulnerability of synaptic vesicles to conditions that affect ion gradients or ion transport systems in the vesicle membranes. This integrated concept,[11] which we will refer to as the pump–leak hypothesis, we now wish to revive and relate to a broader range of anaesthetic processes in the whole organism.

Living cells, using metabolic energy and a variety of transport processes, maintain well-defined internal compositions that are different from the external environment. A cell uses these gradients in many ways: some are fundamental to survival, whereas others are used for more specialized functions. For instance, specialized intracellular compartments such as mitochondria, lysosomes and synaptic vesicles in neurones also have defined internal compositions. In synaptic vesicles, the homeostatic state is maintained by metabolic activity which supplies ATP to ion transport enzymes. These in turn generate ion gradients across the vesicle membrane. One such ubiquitous process is inward proton transport by ATP-dependent enzymes in synaptic vesicle membranes. The resulting pH gradients, acid inside, are used to drive the accumulation of neurotransmitters into the vesicles. If the metabolic balance between production and loss of energy is modified to the extent that the gradients are not sustained, it follows that synaptic vesicles will lose some fraction of accumulated neurotransmitters.[12 13]

The proton pump–leak hypothesis we put forward is that hypoxia (from whatever cause), temperature excursions, pressure, and the colligative effect of anaesthetics acting individually or in concert on specific cellular functions of the whole animal, will alter the ionic gradients of synaptic vesicles such that normal function is compromised. Hypoxia in the nervous system will clearly reduce the availability of ATP generally required by ion pumps. There will be little immediate effect on membrane receptors or the ionic concentration gradients across nerve cell plasma membranes. However, it is likely that the much smaller compartments of synaptic vesicles will quickly lose their ability to maintain ion gradients necessary for full function of synaptic transmission, leading to anaesthesia.

Cold will reduce the rate at which enzymes in the synaptic vesicle membrane can transport ions against a continuing leak, again resulting in compromised function caused by loss of neurotransmitters. Higher temperatures in turn will increase lipid bilayer permeability to ions to an extent that cannot be compensated by increased transport rates, with the same result. Significantly, it is known that volatile anaesthetics also increase bilayer permeability to ions[14] and measurably increase ionic permeability of synaptic vesicles even at concentrations referred to as 'clinical'.[12] One of the authors[15] has questioned whether the permeability increase caused by clinical concentrations of anaesthetics is sufficient to inhibit synaptic vesicle function during neurotransmission. The question cannot be answered because we do not know how sensitive neurotransmission is to small changes in ionic permeability.

Perhaps most significant to the pump–leak concept is that anaesthetic effects in whole animal systems contradicted the thermodynamic prediction of the lipid perturbation model. That is, goldfish, when cooled, actually required less (and at the end no) anaesthetic to produce anaesthesia.[16] It was this observation that prompted the pump–leak hypothesis, leading us to ask whether a lipid site or a protein site by itself can provide a broadly applicable mechanism for anaesthesia. We think not. Although it

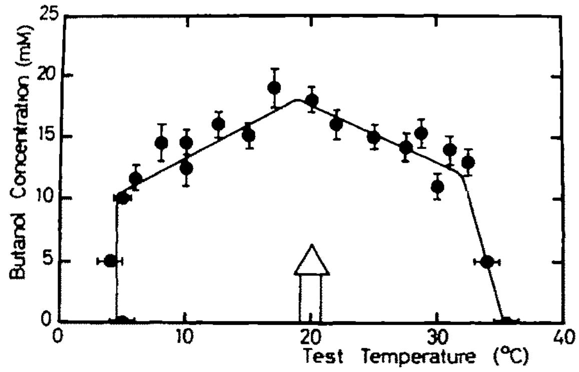

Fig 1 Concentration of butanol required to give zero success (100% avoidance and escape) in 20°C adapted goldfish at a range of test temperatures. Arrow indicates acclimation temperature. Error bars indicate estimated errors from concentration response curves (vertical) or the temperature response curve (horizontal)[14 16]

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is amply demonstrated that a specific anaesthetic acting on a specific receptor on a given cell can be understood as leading to cellular anaesthesia, this obviously cannot account for the anaesthetic effects of hypoxia and temperature excursions on the whole organism. We believe that further tests of the pump–leak concept are warranted, particularly taking into account the predicted relation between anaesthetic action and energy metabolism, ion transport and lipid bilayer permeability noted here

A Bangham
Great Shelford
Cambridge
UK

D Deamer
Department of Chemistry and Biochemistry
UC Santa Cruz
USA

1 Franks NP, Lieb WR Molecular mechanisms of general anaesthesia. *Nature* 1982; **300**· 487–93
2 Franks NP, Lieb WR. Do general anaesthetics act by competitive binding to specific receptors? *Nature* 1996; **310**: 599–602
3 Franks NP, Dickenson R, de Sousa SLM, Hall AC, Lieb WR. How does Xenon produce anaesthesia? *Nature* 1998; **396**. 324
4 Franks NP. Structural basis for the inhibition of firefly luciferase by a general anaesthetic *Biophys J* 1998; **75**. 2205–11
5 Mihic S, Ye Q, Wick M, Koltchine V, Krasowski M, Finn S, Mascia M, Valenzuela C, Hanson K, Greenblatt E, Harris R, Harrison N. Sites of alcohol and volatile anaesthetic action on $GABA_A$ and glycine receptors. *Nature* 1997; **389**. 385–9
6 Mizobe T, Maghsoudi K, Sitwala K, Tianzhi G, Ou J, Maze M. Antisense technology reveals the α_{2A} adrenoceptor to be the subtype mediating the hypnotic response to the highly selective agonist, Dexmedetomidine in the Locus Coeruleus of the rat *JCI* 1986; **98**. 1076–80
7 Lakhlani PP, MacMillan LB, Guo TZ, McCool BA, Lovinger DM, Maze M, Limbird LE. Substitution of a mutant α_{2a}-adrenergic receptor via 'hit and run' gene targeting reveals the role of this subtype in sedative, analgesic, and anesthetic-sparing responses in vivo. *Proc Natl Acad Sci USA* 1997, **94**: 9950–5
8 Sandberg WS, Dubois BW, Miller KW 100 years since Ernest Overton. In: Deamer DW, Kleinzeller A, Fambrough DM, eds. *Membrane Permeability* San Diego, CA: Academic Press, 1999; 311
9 Lee JA, Atkinson RS *A Synopsis of Anaesthesia*, 6th edn Bristol Wright Publishers, 1968; 724
10 Johnstone H. Eton boy died in fainting game *The Times* (*London*) March 17 1999, 3
11 Miller K. Models of consciousness. *Nature* 1986; **323**: 584
12 Bangham AD, Mason W. Anaesthetics may act by collapsing pH gradients. *Anesthesiology* 1980; **53**: 135–41
13 Barchfeld G, Deamer DW The effect of general anesthetics on the proton and potassium permeabilities of liposomes. *Biochim Biophys Acta* 1985; **819**: 161–9
14 Bangham AD, Hill MW. The proton pump/leak mechanism of unconsciousness. *Chem Phys Lipids* 1988; **40**; 189–203
15 Akeson MA, Deamer DW. Steady-state catecholamine distribution in chromaffin granule preparations: a test of the pump-leak hypothesis of general anaesthesia. *Biochemistry* 1989, **28**: 5120–7
16 Bangham AD, Hill MW, Mason WT. A biochemical and biophysical view of anesthesia. *Prog Anesthesiol* 1980, **2**: 69–77

Inappropriate methods for patient satisfaction

Editor—The prospective study by Myles and colleagues,[1] addressing patient satisfaction after anaesthesia and surgery, covers a major field of interest in the evaluation of outcomes in anaesthesia. The size of the sample is impressive and denotes considerable effort to represent the population of patients concerned Yet, despite the endeavour to present compelling results on patient satisfaction, important methodological pitfalls were overlooked.

There is no mention of the criteria employed for the selection of patients. The variable 'patient satisfaction', considered as a major outcome, was measured by a question with only three choices of answer, and results dichotomized between satisfied *vs* somewhat dissatisfied–dissatisfied Such strategy is not very well considered,[2] and it does not generate enough variance in the distribution of the data collected. In addition, services offered by anaesthetists include many components. We doubt that such a complex issue can be properly evaluated by only one question.

Even though the authors recognize the influence of social desirability (eager to please investigator) on respondents, no measures were taken to control for this important confounding variable. Social desirability is more likely to influence older patients (>65 years),[3] and most likely contributed significantly to the final results since this patient population constitutes close to 37% of the sample presented.

Evaluation of patients' perceptions of satisfaction within 24 h of surgery may well be premature. In the immediate postoperative period, patients may still be under the effects of sedative or analgesic drugs (residual effects), especially patients undergoing orthopaedic (18.9%), cardiothoracic (12.4%), neurosurgical (7.6%), plastic (5.3%) or burn (1.8%) procedures.

Such a large sample would have benefited from proper methods The use of sub-optimal methods casts a serious doubt on the results reported (overall level of satisfaction of 96 8%) As an anaesthetist once wrote·[4] 'This apparent satisfaction (high level) should therefore give the anaesthetist little cause for self-congratulation, since it implies that the patient neither expects nor demands a high standard of service or expertise from his anaesthetist...'. We propose that the apparent satisfaction with anaesthesia is not related to patient demands or expectations, but to the use of inappropriate methods. The (inappropriate) methods employed may mislead many readers unfamiliar with research protocols regarding evaluative studies into believing that services provided by anaesthetists have little influence on overall patient satisfaction with their surgical experience.

In conclusion, regardless of the number of respondents in a study, only valid methods (including appropriate sample size) and control of major confounding variables can generate credible results and guide future meaningful researches on this important subject

S. Le May[1]
J.-F. Hardy[1]
M -C. Taillefer[2]
G. Dupuis[2]
[1]*Department of Anaesthesia*
[2]*Department of Psychosomatics Heart Institute*
Montreal
Canada

1 Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery. results of a prospective survey of 10 811 patients. *Br J Anaesth* 2000; **84**: 6–10
2 Crocker L, Algina J. *Introduction of Classical and Modern Test Theory* Montreal: Harcourt Brace Jovanovich College Publishers, 1986
3 Williams B Patient satisfaction: a valid concept? *Soc Sci Med* 1994; **38**. 509–16
4 Keep PJ, Jenkins JR. From the other end of the needle. The patient's experience of routine anaesthesia. *Anaesthesiology* 1978, **33**. 830–2

Editor—Thank you for the opportunity to reply to the letter from Le May and colleagues. We appreciate their interest and agree with a number of issues raised. Some of these were briefly addressed in our original paper. Measurement of satisfaction is indeed difficult and is certainly influenced by expectations. More extensive and complex instruments have been described, but these are unsuitable for routine quality assurance (QA) activities. The decision to dichotomize the degree of satisfaction (or dissatisfaction) is in our opinion justified. An expression of satisfaction requires the patient to make a judgement and incorporates their expectation of care. The construct validity is supported by the strong association between dissatisfaction, awareness, pain, emesis and other complications. Our dissatisfaction rate may well be an underestimate, but it does provide valuable information for us to consider: associated factors may be prevented or better treated. This was the purpose of our paper.

We included all patients who had been surveyed on the morning after surgery (as part of our routine QA activities). The purpose of our QA is to identify deficiencies in care, monitor aspects of recovery and patient satisfaction, and, ultimately, improve the care of our patients. Selection bias was minimized in our study because we included all eligible patients. There were no other selection or exclusion criteria. Inevitably, this does bias the sample of 10 811 towards patients having more major surgery. Timing is an important consideration. We accept that some patients were unable to provide a clear assessment of their care, but we intentionally interviewed them on the morning after surgery so that aspects of our care can be rated. Later review may be more valid, but this may be confounded by later (non-anaesthetic) events.

Patient satisfaction is one of several important outcomes of anaesthetic care. Other methods or instruments, particularly if used in conjunction, will certainly provide a more complete and precise evaluation. We encourage others to develop and validate their use and to pursue patients' assessment of their care.

P S Myles
A. M. Weeks
Department of Anaesthesia and Pain Management
Alfred Hospital
Melbourne
Australia

EEG-controlled rapid opiate detoxification under general anaesthesia

Editor—The short communication by Hensel, Wolter and Kox on rapid opioid withdrawal under general anaesthesia[1] makes no mention of the dangers of the technique, which remains controversial. In April 1998, the Home Office made the following statement on this matter that was reproduced in the President's statement in the July 1998 Royal College of Anaesthetists' Newsletter. 'The Advisory Council on the Misuse of Drugs (ACMD) concluded in the light of the available research literature that the effectiveness and safety of rapid anaesthetic-antagonist detoxification as a treatment method had not yet been established and that the risks attached to the treatment currently appeared to outweigh its benefits. Doctors who practice the treatment could be vulnerable to claims of medical negligence from any patient who suffered complications after treatment. Such claims would be difficult to defend in the light of the findings of the ACMD.'

Anaesthetists who are tempted to use this technique should therefore bear this statement in mind.

D. J. Hatch
Portex Department of Anaesthesia
Institute of Child Health
London
UK

1 Hensel M, Wolter S, Kox WJ. EEG-controlled rapid opioid withdrawal under general anaesthesia. *Br J Anaesth* 2000; **84**: 236–8

Editor—We appreciate the points made by Professor Hatch concerning our article. We are fully aware of the President's statement from the Royal College of Anaesthetists and share the concerns about the safety of this detoxification method in the wrong hands or the wrong environment. However, so far we have used this method for the detoxification of 140 drug addicts and have come to a slightly different view. Recently, we were able to show in a prospective study that rapid opiate detoxification under general anaesthesia is a safe and efficient method to suppress withdrawal symptoms.[1] However, when using opiate receptor antagonists and anaesthetic techniques to facilitate rapid detoxification and suppress withdrawal symptoms, serious adverse events such as pulmonary oedema, cardiovascular impairment, inadvertent anaesthetic overdose, or aspiration may occur.[2 3] In most of the cases, tracheal intubation was not performed or inappropriately high doses of anaesthetics or opiate antagonists given.[4]

Summarizing the literature and our experience we recommend that the treatment should be performed by experienced anaesthetists or intensivists, with qualified nursing care present throughout the procedure. Second, continuous monitoring of vital organ function is essential. The basic monitoring should involve measurements of heart rate, invasive arterial blood pressure, pulse oximetry, end-tidal carbon dioxide, respiratory rate, body temperature and central venous pressure. Gastrointestinal secretion and urine output should be recorded, and blood gas analyses and plasma concentrations of sodium, potassium, glucose and lactate should be measured.

M. Hensel
Department of Anaesthesiology and Intensive Care
University Hospital Charité
Berlin
Germany

1 Hensel M, Kox WJ. Safety, efficacy, and long-term results of a modified version of rapid opiate detoxification under general anaesthesia: a prospective study in methadone, heroin, codeine and morphine addicts. *Acta Anaesthesiol Scand* 2000; **44**: (in press)
2 San L, Puig M, Bulbena A, Farre M. High risk of ultrashort noninvasive opiate detoxification. *Am J Psychiatry* 1995; **152**: 956
3 Taff RH. Pulmonary edema following naloxone administration in a patient without heart disease. *Anesthesiology* 1983; **59**: 576–7
4 Seoane A, Carrasco G, Cabré L, *et al.* Efficacy and safety of two new methods of rapid intravenous detoxification in heroin addicts previously treated without success. *Br J Psychiatry* 1997; **171**: 340–5

Histaminoid reactions associated with rocuronium

Editor—I was interested to read the report of three histaminoid reactions to rocuronium.[1]

All three patients experienced hypotension, tachycardia, varying difficulty with ventilation and audible wheeze on auscultation, and exhibited an erythematous rash as part of the histaminoid response. It is noteworthy that 'there was some reluctance to administer epinephrine even when the diagnosis of anaphylaxis was clearly suspected'.

In an analysis of 57 critical incidences of anaphylaxis under anaesthesia, Currie and colleagues[2] comment on 'the difficulty in making the diagnosis in the acute phase, especially when there is no obvious cutaneous manifestation' and 'if only one of the signs of hypotension, bronchospasm or skin manifestations (including airway oedema) is noticed, especially if severe, the possibility of allergy must be considered early ...'. What hope is there of achieving this if 'some reluctance' to treat patients with all the signs of a 'classical' reaction?

The problem is clearly in making the diagnosis of an anaphylactic reaction in the acute phase (about 90% occur on induction)[3] and initiating treatment as recommended in the Association of Anaesthetists Guidelines.[4] Perhaps there is concern about the initial use of epinephrine if the patient already has a tachycardia. I note that in two of the three patients, aminophylline was given first, presumably as bronchospasm was perceived to be the most important problem.

If only 36% of patients experiencing an anaphylactic reaction under anaesthesia have bronchospasm (ranging from transient to severe) but 88% show cardiovascular collapse (10% as the sole presenting feature)[3 4] then why not recommend methoxamine as the initial drug of choice? Epinephrine could be given first if the bronchospasm was severe or if it was the sole presenting feature. The first patient described needed methoxamine as well as epinephrine, as did a patient described in a recent letter.[5]

The commonest presenting features in anaphylactic reactions under anaesthesia since 1990[3] have been desaturation, loss of pulse waveform or transient difficulty in inflation. In a so-called 'typical' or 'classical' anaphylactic reaction, terms that are not necessarily helpful, the patient develops a tachycardia. In two recent reports of anaphylaxis to succinylcholine[6 7] the presenting clinical feature was bradycardia whereas in previous reports,[8 9] patients developed a tachycardia, albeit following hyoscine or atropine premedication. Tachycardia may be the commonest response in anaphylaxis but any arrhythmia may occur. Cardiovascular collapse of asystole[10] or bradycardia may be the presenting feature of an anaphylactic reaction under anaesthesia. Two patients without underlying heart disease have survived an anaphylactic reaction (one associated with anaesthesia) following the use of intra-aortic balloon pumping.[11] The problem would appear to be one of primary cardiac dysfunction.

Patients present with varying degrees of pre-existing myocardial and bronchial disease. In addition, they may be taking regular medication, for example ACE inhibitors, H_1, H_2 or β-blockers; may have been given anticholinergic premedicant drugs; and may have had an epidural sited. The response to histamine or other endogenous substance release may not be so predictable, the presenting features may only involve one of the cardiovascular, respiratory or dermatological system; and the response to therapy may not be so effective.

The three cases reported by Neal and colleagues[1] emphasize that delays in diagnosis and in instituting appropriate therapy do occur. The presenting clinical features of an anaphylactic reaction under anaesthesia are diverse and teaching must be less dogmatic if the diagnosis is to be made early and suitable therapy commenced.

R. M. Foxell
Department of Anaesthesia
Dorset County Hospital
UK

1 Neal SMcD, Manthri PR, Gadiyar V, Wildsmith JAW. Histaminoid reactions associated with rocuronium. *Br J Anaesth* 2000; **84**: 108–11

2 Currie M, Webb RK, Williamson JA, Russell WJ, Mackay P. Clinical anaphylaxis. an analysis of 2000 incident reports. *Anaesth Intensive Care* 1993; **21**: 621–5

3 Fisher MM. Anaphylactoid reactions during anaesthesia. In: Prys-Roberts C, Brown BR, eds. *International Practice of Anaesthesia*. Oxford. Butterworth-Heinemann, 1996; 1/85/1–13

4 The Association of Anaesthetists of Great Britain and Ireland. *Suspected Anaphylactic Reaction Associated with Anaesthesia*. 1995, revised edition

5 Higgins DJ, Gayatri P. Methoxamine in the management of severe anaphylaxis. *Anaesthesia* 1999; **54**: 1126

6 Villas Martinez F, Jord A, Garmendia FJ, Navarro JA. Anaphylactic reaction to suxamethonium *Invest Allergol Clin Immunol* 1999; **9**· 126–8

7 Porter JM, Magner J, Phelan D. Anaphylaxis due to suxamethonium manifested at induction of anaesthesia by bradycardia and cardiac arrest. *Ir J Med Sci* 1999; **168**: 99–107

8 Jerums G, Whittingham S, Wilson P. Anaphylaxis to suxamethonium. A case report. *Br J Anaesth* 1967; **39**: 73–7

9 Mandappa JM, Chandrasekhara PM, Nelvigy RG Anaphylaxis to suxamethonium. *Br J Anaesth* 1975; **47**: 523–5

10 Fisher MM, Baldo BA The diagnosis of fatal anaphylactic reactions during anaesthesia: employment of immunoassays for mast cell tryptase and drug-reactive IgE antibodies. *Anaesth Intensive Care* 1993; **21**. 353–7

11 Raper RF, Fisher MM. Profound reversible myocardial depression after anaphylaxis. *Lancet* 1989; i: 386–8

Editor—Thank you for the opportunity to comment on Dr Foxell's letter. In general, he seems to support our views although it is important not to be too critical of the clinicians involved regarding their expectant approaches to the use of epinephrine. All three patients developed a complete picture of anaphylaxis with cardiovascular, respiratory and dermal features, but these features did not all appear immediately or together. Each had to be recognized and the differential diagnoses considered before treatment could be instituted. We do agree absolutely with him on the utility of methoxamine in patients who are both hypotensive and tachycardic.

P. R. Manthri
J. A. W. Wildsmith
University Department of Anaesthesia
Ninewells Hospital & Medical School
Dundee
UK

Comparison of laryngeal mask and intubating laryngeal mask insertion by the naïve intubator

Editor—A secure airway is fundamental to the provision of basic and advanced life support.[1] Whilst the laryngeal mask airway (LMA) offers a useful alternative for untrained staff,[2] the 1998 European Resuscitation guidelines state that the tracheal tube (TT) remains the gold standard.[3] Choyce and colleagues in their study comparing the use of the LMA and the intubating LMA make a bold statement.[4] They suggest that valuable time may be saved by an experienced airway practitioner (by implication an anaesthetist) avoiding direct laryngoscopy and passing the TT down the intubating LMA. We feel that this assertion is probably erroneous and possibly dangerous.

First, whilst all anaesthetists are trained to a high level of skill at performing direct laryngoscopy and tracheal intubation, the intubating LMA is a new device with which many are unfamiliar. This, of course, would be easily remedied by the widespread availability of such devices in all operating theatre suites, accompanied by their use in all cases where insertion of either an LMA or a TT is deemed appropriate. This would have clinical and cost implications which would need to be addressed. In any event, it seems unlikely that a skilled anaesthetist would achieve intubation with a TT any more rapidly by the use of an intubating LMA.

Second, the suggestion that the specific avoidance of direct laryngoscopy in the acute management of the airway is a practice to be actively encouraged appears to us to be worthy of little merit. Current Association of Anaesthetists guidelines suggest that minimal standards of monitoring should include a capnograph.[5] In the absence of the direct observation of the TT passing between the vocal cords, scrutiny of the end-tidal carbon dioxide trace confirms correct placement of a TT. However, during cardiopulmonary arrest, when correct placement of the TT is integral to success, such monitoring equipment is rarely available.

Whilst it is interesting that significantly more participants rated insertion of the intubating LMA as easier than the regular LMA, no comment is made as to which was attempted first. Indeed, although the order of insertion was randomly allocated by means of a toss of a coin, it is not stated whether this led to equal numbers of participants in each group. However, if no bias were introduced at this stage, it would seem reasonable to provide an intubating LMA on resuscitation trolleys, for use by non-anaesthetists. This should not preclude direct laryngoscopic visualization of the TT passing between the vocal cords at the time of intubation.

S. I. Jaggar
C. P. R. Walker
Royal Brompton Hospital
London

1 *Advanced Life Support Course Provider Manual* (3rd edn), Resuscitation Council (UK) 1998
2 The use of the laryngeal mask airway by nurses during cardiopulmonary resuscitation. Results of a multicentre trial. *Anaesthesia* 1994; **49**: 3–7
3 Baskett PFJ, *et al.* Guidelines for the advanced management of the airway and ventilation during resuscitation. *Resuscitation* 1996; 201–30
4 Choyce A, Avidan MS, Patel C, *et al.* Comparison of laryngeal mask and intubating laryngeal mask insertion by the naive intubator *Br J Anaesth* 2000; **84**: 103–5
5 *Recommendations for Standards of Monitoring During Anaesthesia and Recovery.* Revised 1994; Association of Anaesthetists of Great Britain and Ireland, London

Editor—We thank Jaggar and Walker for their comments and would like to discuss some of the issues raised. In our introduction[1] we made the proposition that valuable time could be saved during resuscitation if an experienced airway practitioner intubated the trachea via an intubating laryngeal mask (ILM) already inserted by a non-anaesthetist. We did not set out to investigate any further benefit accrued from reduced time to secure the airway with a tracheal tube. However, the significant benefits of the ILM over the laryngeal mask airway (LMA) that we did show (reduced time to insertion, improved ventilation, preferred device) led us to conclude that there may a place for the ILM in resuscitation. We can only speculate at this point as to whether the anaesthetist called upon to secure the airway perhaps without a pillow, without an assistant, with poor patient position, immovable bed head, etc., would fare better with an ILM. As to what part of this process they feel to be dangerous we are unsure; certainly unfamiliarity with the device should exclude its use as a conduit for tracheal intubation.[2]

We accept that, as a blind technique, one clinical sign of a successful tracheal intubation is lost when using the ILM. However, the anaesthetist trained in its use can expect a success rate of over 90%.[3] Surely other signs of tube placement available to the anaesthetist can be relied upon to remedy the minority of misplaced tubes?

Finally, our method of random allocation of order of device insertion is a potential source of bias. However, we can reassure the correspondents that the numbers inserting each device first differed by only a single participant. It is pleasing that they feel able to justify the presence of the ILM on a resuscitation trolley. We feel that the case is not yet made and are further investigating the use of the ILM in anaesthetized patients

A. Choyce
Toronto Western General Hospital
Canada

1 Choyce A, Avidan MS, Patel C, *et al.* Comparison of laryngeal mask and intubating laryngeal mask insertion by the naive intubator. *Br J Anaesth* 2000; **84**: 103–5
2 Avidans MS, Harvey A, Chitkara N, Ponte J. The intubating laryngeal mask airway compared with direct laryngoscopy. *Br J Anaesth* 1999, **83**: 615–17
3 Kapila A, Addy EV, Verghese C, Brain AIJ. The intubating laryngeal mask airway: an initial assessment of performance. *Br J Anaesth* 1997; **79**: 710–13

Severe vasovagal attack during regional anaesthesia for Caesarean section

Editor—The case report by Watkins and colleagues[1] provides clear illustration of a potential complication of inducing regional anaesthesia with the patient seated. A vasovagal attack, probably superimposed on some degree of sympathetic block, caused severe hypotension which was resistant to treatment and led to some fetal compromise. Our experience, like theirs, is that vasovagal episodes in association with regional anaesthesia are not rare, although we find some clinicians reluctant to accept that it can happen in spite of previous reports in the literature.[2] Rightly, Watkins and colleagues ask how their patient might have been better managed. We have two comments.

First, there is the question of patient position. The optimum position for inducing spinal anaesthesia for Caesarean section has been debated, with advocates of the sitting position citing ease of technique and rapid dural puncture among its advantages.[3] However, the performance of a combined spinal/epidural technique is a more lengthy procedure. These episodes are difficult to predict and can occur in apparently calm individuals with no preceding history of fainting The longer the patient is sitting, the greater must be the risk (and severity) of any such episode. However, the horizontal position is no absolute protection, as Figure 1 demonstrates.

A healthy, 45-yr-old woman received an intrathecal injection of tetracaine (10 mg in 2 ml saline) prior to varicose vein surgery. Lumbar puncture was performed in the lateral position, and was entirely straightforward, but when she was placed supine she was found to have severe nausea, pallor, bradycardia and an unrecordable blood pressure. Atropine 0.6 mg, followed by ephedrine 15 mg, both i.v., produced some increase in pulse rate and a recordable blood pressure, but no real improvement. The concern was of a total spinal, but the block was no higher than the inguinal ligament. At this time, an apology arrived from the ward staff regarding accidental omission of the premedication (temazepam 10 mg) and prompted administration of a small dose of thiopental (50 mg), the most immediately available sedative. The effect on all clinical variables was dramatic: pulse, blood pressure and peripheral circulation were restored, and the nausea stopped. After a few minutes, the blood pressure started to decrease again and the nausea recurred so a further two doses of thiopental 50 mg were given and caused the patient to sleep, uneventfully, through her operation.

Thus the second issue is the role of anxiolytic drugs in the

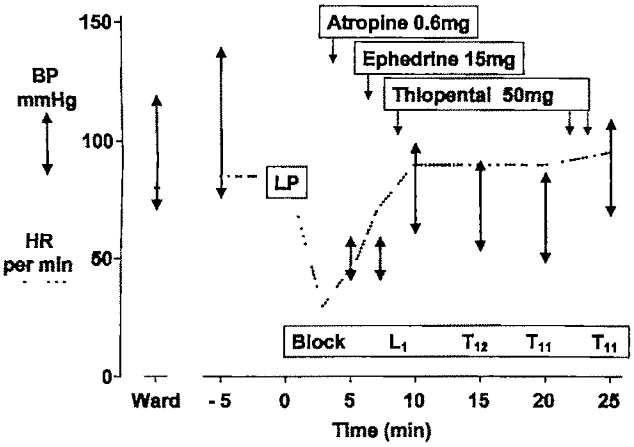

Fig 1 Summary of a vasovagal attack during induction of spinal anaesthesia.

prevention and treatment of such episodes. Clearly, the issue must be approached with caution because other causes of hypotension during induction of regional anaesthesia might be exacerbated by administration of central nervous system depressants. However, we feel that the key feature seen in this patient (and other less severe cases), was the association of nausea with bradycardia, both responding to quite low doses of sedative. Premedication exerts a protective effect and its use is to be encouraged. This might not be acceptable in the obstetric situation, but a small dose of i.v. benzodiazepine (e.g. midazolam 1 mg) as treatment, if not for routine prevention, of such events is unlikely to affect the baby significantly.

D. Burke
J. A. W. Wildsmith
University Department of Anaesthesia
Ninewells Hospital & Medical School
Dundee
UK

1 Watkins EJ, Dresner M, Calow CE Severe vasovagal attack during regional anaesthesia for Caesarean section. *Br J Anaesth* 2000; **84**: 118–20
2 McConachie I. Vasovagal asystole during spinal anaesthesia *Anaesthesia* 1991; **46**: 281–2
3 Serpell MG, Carson DF. Maternal position during induction of spinal anaesthesia for Caesarean section. *Anaesthesia* 1995; **50**. 921–2

Editor—Watkins, Dresner and Calow describe an episode of severe and resistant hypotension in a patient undergoing Caesarean section under regional anaesthesia.[1] They describe an event which, in its milder form at least, is a common occurrence in obstetric anaesthesia. They convey the feeling of impending terror we all have when initial measures fail to rectify this situation and their case highlights the potential neonatal morbidity associated with prolonged maternal hypotension. I would like to comment on one aspect of their management.

I wonder why they chose to continue to give ephedrine once the initial 30 mg had failed to work. They state that they went on to give another 40 mg in divided doses. Ephedrine acts partly by direct stimulation of α-receptors and partly by displacing norepinephrine from sympathetic nerve endings. Tachyphylaxis is a well-known characteristic of ephedrine because of depletion of noradrenergic stores. Repeated doses in the face of a poor response bring diminishing returns.

In my experience, if ephedrine 30 mg has failed to produce an appreciable or sustained effect, further doses do not help. In such an event, and given that the patient has a normal heart rate and adequate intravascular volume, it is my practise to give a small dose of a pure α-agonist, such as methoxamine 2 mg or metaraminol 1 mg. I find it is relatively unusual to have to give more than one or two such boluses to achieve an acceptable blood pressure. A straw poll amongst my colleagues confirms that I am not alone in this practice. Impairment of uterine blood flow is a commonly quoted relative contraindication to the use of pure α-agonists prior to delivery of the fetus. However, in this case report, the patient was in a precarious situation, with periods of 'severe hypotension and near syncope'.

The authors opt for the diagnosis of 'a combination of vasovagal reflex with spinal-induced sympathectomy'. However, the patient's heart rate was 80 beat min^{-1}, could it not simply be that this was a spinal-induced sympathectomy which was incompletely treated? I wonder if the authors made a conscious choice not to use a direct α-agonist in this case and if so, why?

T. Meek
Royal Victoria Infirmary
Newcastle-upon-Tyne
UK

1 Watkins EJ, Dresner M, Calow CE. Severe vasovagal attack during regional anaesthesia for Caesarean section. *Br J Anaesth* 2000, **84**. 118–20

Spinal anaesthesia in children: are we missing the point?

Editor—We would welcome the opportunity to comment on the study by Kokki and Hendolin.[1] We appreciate that this study was designed primarily to evaluate the role of baricity in block characteristics but question what benefits are gained by using this technique in healthy children.

The remit of any anaesthetist called upon to anaesthetize a child must be to create ideal operating conditions safely whilst causing the least possible distress to the child. Stress at induction of anaesthesia has been shown to cause postoperative behavioural problems.[2] In recent years studies have shown that parental presence at induction reduces stress,[3] [4] and that even after the administration of a premedicant, 10–20% of children are still distressed by parental separation.[5]

Drs Kokki and Hendolin point out that despite a reasonable anxiolytic premedicant, approximately 50% of children felt uncomfortable, or expressed a wish for further sedation. The authors looked at a wide age range but made no comment as to whether the age of the child had a bearing on the requirement for further anxiolysis. The authors state that the advantages of the spinal technique are rapid onset, profound and uniformly distributed analgesia and good neuromuscular blockade We would suggest that a balanced general anaesthetic technique would also achieve these benefits and have the added advantage of reliability—spinals in children have failure rates as high as 5–10%[6]—and avoidance of child—parent separation whilst the child is conscious

We appreciate that general anaesthesia is not without risk, but suggest that the morbidity related to spinal anaesthesia is more significant We note that Drs Kokki and Hendolin quote a 5% incidence of hypotension requiring treatment, and a 6% incidence of bradycardia requiring treatment with atropine. Other studies have highlighted the greater incidence of cardiovascular instability in children over 5 yr old.[7] Also the incidence of postdural puncture headache has been reported to be between 5 and 50% in children over 8–10 yr old.[6]

The anaesthetist's responsibility also extends into pain control postoperatively. For surgical procedures below the umbilicus the gold standard must be epidural analgesia, be this via a one shot caudal or a catheter in the lumbar region. Unfortunately, none of the children in this study were able to benefit from this technique. Whereas it may be reasonable to expect adolescents and young adults to give informed consent to a spinal anaesthetic, we would question the ability of 7- to 12-yr-olds to fully comprehend the concept of the technique and therefore be in a position to give informed assent.

D. P. Prosser
Department of Anaesthesia
Bristol Children's Hospital
UK

T. K. Howell
Department of Anaesthesia
Royal Manchester Children's Hospital
UK

1 Kokki H, Hendolin H. Hyperbaric bupivacaine for spinal anaesthesia in 7–18 yr old children: comparison of bupivacaine 5 mg/ml in 0.9% and 8% glucose solutions. *Br J Anaesth* 2000; **84**: 59–62
2 Eckenhoff JE. Relationship of anesthesia to post-operative personality changes in children. *Am J Dis Child* 1953; **86**: 587–91
3 Kam PC, Voss TJ, Gold PD, *et al.* Behaviour of children associated with parental participation during induction of general anaesthesia. *J Paediatr Child Health* 1998; **34**: 29–31
4 Cameron JA, Bond MJ, Pointer SC. Reducing the anxiety of children undergoing surgery: parental presence during anaesthetic induction. *J Paediatr Child Health* 1996; **32**: 51–6
5 Alderson PJ, Lerman J. Oral premedication for paediatric ambulatory anaesthesia: a comparison of midazolam and ketamine. *Can J Anaesth* 1994; **41**: 221–6
6 Tobias JD Spinal anaesthesia in infants and children. *Paediatr Anaesth* 2000; **10**: 5–16
7 Dohi S, Naito H, Takahashi T. Age related changes in blood pressure and duration of motor blockade in spinal anesthesia. *Anesthesiology* 1979; **50**: 319–23

Editor—We are pleased that our study of spinal anaesthesia has generated interest. As Prosser and Howell noted the aim of our study was to evaluate the role of baricity in block characteristics. The failure rate of spinal anaesthesia in these patients was 4%. However, none of the children needed conversion to general anaesthesia to complete surgery. Moreover, the incidence of postdural puncture headache was 4%, and in all children the symptoms resolved in 1 or 2 days: none needed an epidural blood patch.[1]

We agree with Prosser and Howell that general anaesthesia is not without risk,[2] and that the anaesthetist's responsibility also extends into pain control postoperatively.[3 4] We therefore use epidural analgesia with a lumbar or thoracic catheter after major surgery[5 6] ('the gold standard') and after minor surgery we use peripheral blocks combined with proactive pain treatment with non-opioid analgesics.[3 4 7]

In those children who have a history of hypotension and/or bradycardia due to extended sympathetic block after spinal anaesthesia we would use a smaller dose of bupivacaine, 0.2 mg kg^{-1} instead of 0.3 mg kg^{-1} in future, if required.

H. Kokki
Kuopio University Hospital
Kuopio
Finland

1 Kokki H, Hendolin H. Hyperbaric bupivacaine for spinal anaesthesia in 7–18 yr old children: comparison of bupivacaine 5 mg/ml^{-1} in 0.9% and 8% glucose solutions. *Br J Anaesth* 2000; **84**: 59–62
2 Kokki H, Hendolin H, Vainio J, Partanen J. Operation im Vorschulalter. Vergleich von Spinalanasthesie und Allgemeinanasthesie. *Anaesthetist* 1992; **41**: 765–8
3 Sepponen K, Kokki H, Ahonen R. Training of medical staff positively influences postoperative pain management at home in children. *Pharm World Sci* 1999; **21**: 168–72
4 Nikanne E, Kokki H, Tuovinen K Postoperative pain after adenoidectomy in children. *Br J Anaesth* 1999; **82**: 886–9
5 Kokki H, Tuovinen K, Hendolin H. Intravenous ketoprofen and epidural sufentanil analgesia in children after combined spinal-epidural anaesthesia. *Acta Anaesthesiol Scand* 1999; **43**: 775–9
6 Kokki H, Tuovinen K, Hendolin H. The effect of intravenous ketoprofen on postoperative epidural sufentanil analgesia in children. *Anesth Analg* 1999; **88**: 1036–41
7 Kokki H, Hendolin H, Maunuksela EL, Vainio J, Nuutinen L Ibuprofen in the treatment of postoperative pain in small children. A randomized double-blind placebo controlled parallel group study. *Acta Anaesthesiol Scand* 1994; **38**: 467–72

Effect of continuous epidural 0.2% ropivacaine *vs* 0.2% bupivacaine on postoperative pain, motor block and gastrointestinal function after abdominal hysterectomy

Editor—We read with interest the paper by Jørgensen and colleagues in which epidural infusion of 0.2% ropivacaine and bupivacaine were compared as analgesia after hysterectomy.[1] Pain scores, use of supplementary analgesics and motor block were evaluated.

The authors found that the two solutions were remarkably similar. However, in the subgroup requiring supplementary analgesia more doses of ketorolac were required by patients in the 0.2% ropivacaine group during the first 24 h. There was also a 'trend' towards increased requests for supplementary morphine and reduced motor block with ropivacaine.

This is another of the many studies that have failed to address differences in potency between ropivacaine and bupivacaine. It is very difficult to assess such differences in the clinical situation. This study uses a common model, which relies upon the number of requests for supplementary analgesia to distinguish between agents This introduces a mass of variables, such as availability and effectiveness of the supplementary agent chosen, which may mask even quite marked differences between agents. A more effective technique establishes the minimal dose required to produce analgesia. In almost all clinical situations, this is unethical. However, in labour, minimal analgesia without any supplementary analgesic is desirable. Two studies have used this model: both Capogna's[2] and Polley's[3] group found that ropivacaine is only 60% as potent an analgesic agent as bupivacaine.

In studies such as this one, where equal concentrations of ropivacaine and bupivacaine are used, any comparison of the effect on motor block and postoperative pain are uninformative. In addition, the previously established differences in safety between the two agents may be confounded by differences in potency.

This is why the studies by Polley and Capogna are important. Surely it is time that studies comparing ropivacaine and bupivacaine routinely assume an analgesic potency ratio of approximately 0.6?

A M Pickford
A. J. Eldridge
Queen Alexandra Hospital
Portsmouth
UK

1 Jørgensen H, Fomsgaard JS, Dirks J, Wetterslev J, Dahl JB. Effect of continuous epidural 0.2% ropivacaine vs 0.2% bupivacaine on postoperative pain, motor block and gastrointestinal function after abdominal hysterectomy. *Br J Anaesth* 2000; **84**: 144–50

2 Capogna G, Celleno D, Lyons G, Columb M. Relative potencies of bupivacaine and ropivacaine for analgesia in labour. *Br J Anaesth* 1999; **82**: 371–3

3 Polley LS, Columb MO, Naughton NN, Wagner DS, Van de Ven CJM. Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labour. *Anaesthesiology* 1999; **90**: 944–50

Editor—We thank Dr Pickford and Dr Eldridge for their comments. We agree with most of their remarks. We thought it was time to make direct comparisons between ropivacaine and bupivacaine with respect to effects on postoperative pain after abdominal surgery. The main problem, as we see it, is not whether ropivacaine is only 60% as potent an analgesic agent as bupivacaine, but if ropivacaine has a more favourable sensory/motor ('differential') block profile than bupivacaine in the clinical situation. Our clinical study did not indicate that this is the case. Problems with power may explain some of the inconclusive results. Future studies should compare the effects of 0.12% bupivacaine with 0.2% ropivacaine in about 250 patients, if anybody believes that it is worth the effort!

H. Jørgensen
J. S. Fomsgaard
J. Dirks
J. Wetterslev
J. B. Dahl
Department of Anaesthesiology and Intensive Care
Herlev University Hospital
Herlev
Denmark

Hidden hazards of scavenging

Editor,—Dr Carvalho's letter on the hidden hazards of scavenging[1] has highlighted a very important problem which all anaesthetists and anaesthesia nurses should be aware of. This is certainly not the first incident and will not be the last.

The photograph in the letter showed an arrangement where the wheel of the anaesthetic machine can be seen occluding the scavenging transfer tubing. I have no doubt that this is a re-enactment. The tubing is connected to the adjustable pressure-limiting valve of the carbon dioxide absorber. Any anaesthetist familiar with the use of the circle circuit will know that only during spontaneous breathing general anaesthesia will the adjustable pressure-limiting valve be left partially opened. Only during such an arrangement will the expiratory resistance be affected by the occlusion of the scavenging transfer tubing. This explains the difficulties encountered during hand ventilation.

During mechanical ventilation, the adjustable pressure-limiting valve of the carbon dioxide absorber should be closed to avoid leakage of gas during positive pressure ventilation. The photograph cannot be used to explain why there was a baseline of 17 cm H_2O during mechanical ventilation. Nevertheless, it was the keen eye of the anaesthetist which prevented any morbidity.

Similar Ohmeda anaesthetic machines are used in our operating theatres. At the back of the machine, there is a handle on either side to facilitate handling of it. The scavenging transfer tubing can be threaded through the handles to secure it. This arrangement will prevent accidental occlusion of the scavenging transfer tubing by the wheels of the anaesthetic machine.

N. C. Hwang
Singapore General Hospital
Singapore

1 Carvalho B. Hidden hazards of scavenging. *Br J Anaesth* 1999, **83**: 532–3

Editor—Thank you for the opportunity to respond to Dr N.C Hwang's comments on my letter. During hand-assisted or spontaneous ventilation, the adjustable pressure-limiting valve is left partially or completely open. As Dr N.C. Hwang has stated, it is only with this arrangement that the effects of occlusion to the scavenging transfer tubing will be appreciated. The increased expiratory resistance in the occluded tube explains the increase in baseline pressure encountered. Once the adjustable pressure-limiting valve is fully closed, the circuit is effectively excluded from the scavenging port and will not be affected by similar occlusions to the scavenging tube.

During mechanical ventilation, the scavenging is specific to the anaesthetic machine and its assembly. The adjustable pressure-limiting valve is closed or bypassed when converting to a mechanical ventilation mode. Scavenging then occurs directly from the ventilator to the main scavenging transfer tubing or reservoir. The assembly of our ventilator scavenging involved a T-piece connection to the main scavenging transfer tubing which was excluded from the photograph for simplification in demonstrating the wheel occlusion. Whether or not occlusion of the scavenging tubing affects both spontaneous and mechanical ventilation is dependent on the site of occlusion. In my case, the obstruction was distal to the T-piece connection and therefore affected both modes of ventilation.

Many of the newer machines eliminate this risk completely. For example with the Datex Engstrom AS/3®, the pipeline scavenging hose is connected directly to the back of the machine with the tubing and reservoir contained within the machine But it must be stressed that despite these efficient safety mechanisms and machine designs, there is no substitute for vigilance in the operating theatre.

B Carvalho
Royal Devon and Exeter Hospital
Exeter
UK

Contamination of saline

Editor—In the course of developing a new indicator (Li^+) dilution method of measuring cardiac output, we have encountered a problem due to a contaminant contained in bags of saline supplied for infusion in man.

Lithium dilution cardiac output (LiDCO) is determined by injecting a small dose of lithium chloride (1–2 ml of 150 millimolar solution) intravenously and recording its arterial dilution curve by withdrawing blood (at 4.5 ml min^{-1}) past a lithium-selective electrode which was developed for this application.[1 2] The method has been given FDA approval and has the advantages of being simple to use and of avoiding the risks of pulmonary artery catheterization (for full details see www.lidco.com). The electrode is in a flow-through cell which is filled with saline except when making a measurement. Figure 1 shows two curves. The larger curve represents the change in the electrode membrane potential when uncontaminated saline is replaced by saline from a bag supplied for intravenous infusion (Baxter Healthcare Ltd). The voltage drifts in a positive direction and the sensitivity of the electrode to Li^+ is greatly reduced, so that the sensor is unusable. Saline solution made up with sodium chloride bought from a grocer (J. Sainsburys plc) and London tap water has no such effect. The smaller curve was obtained while measuring cardiac output in a patient. It shows the change in membrane potential produced by a bolus intravenous injection of lithium chloride 0.3 mmol as arterial blood was withdrawn past a lithium electrode This curve represented a cardiac output of 4.4 litre min^{-1} and a peak lithium concentration of 0.5 mM. It is included in the figure

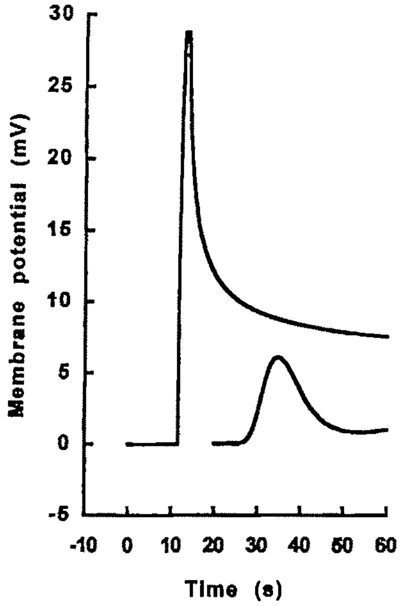

Fig 1 Plot of the lithium electrode membrane potential during replacement of uncontaminated saline with Baxter's saline (larger curve), and during determination of cardiac output by lithium dilution (smaller curve).

in order to put the magnitude of the effect of the Baxter saline contaminant in context.

Further investigation showed that the source of the contaminant is the outer plastic pouch in which the bag of Baxter's saline is contained. Baxter Healthcare Ltd supplied us with bags of saline which had never been in an outer pouch. Saline from these bags had no adverse effect on the sensor, but when a small square of the pouch material was put into saline from one of these bags (which had never been in an outer pouch), heated and then cooled (as in an autoclave cycle), it had a similar effect on the sensor to that shown in Figure 1. The conclusion is that there is a substance present in the outer pouch which diffuses through the inner bag into the saline solution. The pouches used in the USA do not have this effect.

This finding generates concern about the diffusion of foreign substances through the wall of the inner bag. Workers who require pure saline should not assume that commercially produced bags of saline contain nothing more than Na^+, Cl^- and water. We have no proof that the contaminant (as yet unidentified) is harmful to man but one cannot assume that it is safe. It is not only lithium-selective electrodes that have membranes!

R A. F. Linton
D M Band
The Rayne Institute
St Thomas' Hospital
London
UK

We are directors of Monitoring Technology Ltd and LiDCO Ltd, which are the companies responsible for the development of this method of measuring cardiac output

1 Linton R, Band D, O'Brien T, Jonas M, Leach R. Lithium dilution cardiac output measurement: a comparison with thermodilution. *Crit Care Med* 1997, **25**: 1796–800
2 Linton RAF, Band DM, Haire KM. A new method of measuring cardiac output in man using lithium dilution. *Br J Anaesth* 1993; **71**: 262–6

Acute dystonia in a 14-yr-old following propofol and fentanyl anaesthesia

Editor—Propofol and fentanyl are commonly used anaesthetic agents. We report a case of acute dystonia following administration of this combination of drugs for day-case surgery. A 14-yr-old girl, weighing 44.5 kg, received intravenous (i.v.) propofol 130 mg and fentanyl 50 µg as general anaesthesia for dental extractions. She had received the same combination of drugs for myringotomies 10 and 15 months previously, without incident. She had no past history of motor difficulties, seizures or substance abuse and was not on any medication pre-operatively. Ten minutes after returning to the ward, while still asleep, she developed gross non-rhythmic, non-symmetrical jerky upper and lower limb movements which continued for several minutes. She was treated sequentially with diazepam 10 mg per rectum, diazepam 15 mg i.v. and paraldehyde 17 ml per rectum. Her abnormal limb jerking continued, but with less frequency, and it was decided to halt further anticonvulsant treatment. Serum electrolytes, calcium, magnesium, glucose, liver enzymes, lactate, ammonia, bicarbonate, full blood count and coagulation screen were unremarkable. Urgent cerebral CT scan was normal. Over the next 6 h, her conscious level returned to normal. Review by a paediatric neurology consultant concluded that her abnormal movements were dystonic. Treatment with procyclidine 2.5 mg i.v. produced transient and incomplete resolution of her symptoms. After three days, her abnormal movements abated completely. An EEG, performed 70 h after anaesthesia, showed no epileptiform activity but did show some non-specific slow wave and theta activity, consistent with sedative drug treatment.

Abnormal movements following anaesthesia may be difficult to differentiate. Seizures following propofol anaesthesia are well recognized in adults[1] and have been reported in paediatric patients given propofol alone,[2] and in combination with fentanyl.[3] However, the only specific report of *dystonia* following propofol concerns an adult with a pre-existing torticollis-dystonia disorder.[4] Dystonia following fentanyl anaesthesia has been reported in an adult with untreated Parkinson's disease[5] and in one other adult case.[6]

Our 14-yr-old patient appears to have had an acute dystonic reaction to the combination of propofol and fentanyl. This has not, to our knowledge, been previously reported in a child (Medline search, 1966 to present, using keywords 'propofol' explode/focus, 'fentanyl' explode/focus, 'dystonia' explode/focus, in all combinations). Her abnormal movements were initially misinterpreted as seizures and did not respond to conventional anticonvulsant therapy. Clinicians need to be aware of this potential side-effect so that accurate diagnosis can be made, thereby avoiding inappropriate investigation and drug treatment for abnormal movements.

R. Bragonier
D. Bartle
S. Langton-Hewer
Royal Hospital for Sick Children
Bristol
UK

1 Sutherland MJ, Burt P. Propofol and seizures. [Review]. *Anaesth Int Care* 1994; **22**: 733–7
2 Bendiksen A, Larsen LM. Convulsions, ataxia and hallucinations following propofol. *Acta Anaesthesiol Scand* 1998; **42**: 739–41
3 Finley GA, MacManus B, Sampson SE, Fernandez CV, Retallick R. Delayed seizures following sedation with propofol. *Can J Anaesth* 1993; **40**: 863–5
4 Zabani I, Vaghadia H. Refractory dystonia during propofol anaesthesia in a patient with torticollis-dystonia disorder. *Can J Anaesth* 1996; **43**: 1062–4

5 Mets B. Acute dystonia after alfentanil in untreated Parkinson's disease. *Anesth Analg* 1991; **72**: 557–8
6 Khan ZH. Dystonic movements following thalamonal and alfentanil induction–a case report. *Mid East J Anesth* 1998; **14**: 281–6

Laparotomy following femoral venous line insertion

Editor—We report an unusual complication of femoral venous cannulation. A 35-yr-old man was admitted to casualty with superficial stab wounds to his neck and epigastrium. He was an intravenous drug user and securing venous access had been difficult for the accident and emergency staff He had had a large-bore, long left femoral venous line inserted and a 14G Venflon inserted into his right long saphenous vein. He was given 2 litres of crystalloid via the femoral line in casualty. He was oozing continuously from his left sided neck wound and a haematoma had developed subcutaneously. The wound in his epigastrium was explored by a surgeon in casualty who felt that it did not penetrate the muscle layer. No other injuries were identified although the patient had had a left-sided intercostal drain inserted following a left-sided needle thoracocentesis in case the injury to the neck had caused a pneumothorax. The thoracocentesis did not reveal blood, fluid or air in the pleural cavity. We were told that the patient required surgery immediately to explore his neck wound.

On arrival in the operating theatre his pulse was 55 beat min^{-1} and arterial pressure 90/55 mm Hg. He was drunk (it was New Years Day) but denied having taken any other recreational drugs recently. We did not anticipate any problems with tracheal intubation and performed a rapid sequence induction with etomidate and succinylcholine. The drugs were administered via the 14G Venflon in his right saphenous vein. His arterial pressure fell after induction to 65/40 mm Hg. We connected a 'Level 1' pressurized, warmed, rapid infusion system to the left femoral line and rapidly infused 2 litres of colloid and 2 units of blood over a 5-min period. During this time, his lower abdomen was visibly distending. We decided that a laparotomy was needed immediately and assumed that the epigastric wound was deeper than the initial assessment had suggested. He became bradycardic during infusion of the colloid but atropine 0.6 mg plus 0.6 mg given via the left femoral line did not increase the heart rate. Prior intake of beta blocking agents was considered. At laparotomy, there was some free clear fluid in the abdomen but there was also a very large, fluctuating retroperitoneal mass. It was immediately obvious that the left femoral line was not in the femoral vein but had tracked alongside the femoral vessels into the retroperitoneum. All infusions into the left femoral line were in the retroperitoneum.

The Level 1 pressure system was switched to the 14G Venflon in the right saphenous vein, the laparotomy was closed and the superficial vein in the neck tied off. The patient was woken up and made a full recovery over the next few days. No drainage was made of the retroperitoneal collection, the surgeons assuming that it would be absorbed spontaneously.

This case demonstrates a further complication of central venous line insertion; the problem of using venous lines placed by other practitioners; and the danger of high-pressure infusion systems when the cannula is not in the vein.

S. Tomlinson
L. Stannard
Salford
UK

Fractured femur in the elderly

Editor—We read the editorial by Sharrock[1] and the case report by Oliver and colleagues with interest.[2] The case report refers to the management of a femoral shaft fracture and the editorial deals exclusively with the management of femoral neck fractures. The views in the editorial are personal and are based on the American experience as opposed to that of other countries or an evidence-based belief.

It may be that more intensive perioperative assessment and monitoring may improve outcome for this group of patients as was suggested in some small studies in selected groups of patients.[3 4] There is limited evidence on the effect of anaesthetic technique on outcome in fractured neck of femur surgery.[5] Well-conducted studies in large numbers of patients are needed to see if different aspects of preoperative preparation and perioperative care will improve outcome.

There has been a dedicated hip fracture service in Peterborough since 1987 and this multidisciplinary approach aiming for early resuscitation, operation and rehabilitation has brought about dramatic improvements in morbidity and mortality.[6] This has been achieved without the need for an intensive or high dependency service, which are in great demand in the NHS During the last 12 years, 17 patients over 100 yr old have been treated with fractured necks of femur. The age range was 100–103 yr and we have the following follow-up data. Fifteen patients were treated operatively: seven had dynamic hip screws, seven had Austin Moore prostheses and one had AO screws. Six received general anaesthesia and nine spinal anaesthesia, none were admitted to the ITU. Three patients died within 30 days, seven had died by 90 days and at the end of a year ten had died leaving seven survivors. Five of the deaths occurred in hospital. Twelve patients were returned home, mainly to residential care. The aim of the Peterborough service is fast track care and almost all of the operations are done by a dedicated surgeon (MP) with anaesthesia provided by consultants in day-light hours.

R. Griffiths
M. Parker
Departments of Anaesthesia and Orthopaedic Surgery
Peterborough District Hospital
Peterborough
UK

1 Sharrock NE. Fractured femur in the elderly: intensive perioperative care is warranted. *Br J Anaesth* 2000; **84**: 139–40
2 Oliver CD, White SA, Platt MW. Surgery for fractured femur and elective ICU admission at 113 yr of age. *Br J Anaesth* 2000; **84**: 260–2
3 Sinclair S, James S, Singer M. Intraoperative intravascular volume optimization and length of hospital stay after repair of proximal femoral fracture; randomised control trial. *Br Med J* 1997; **315**: 909–12
4 Schultz RJ, Whitfield GF, Lamura JJ, Raciti A, Krishnamurthy S The role of physiologic monitoring in patients with fractures of the hip. *J Trauma* 1985; **25**: 309–17
5 Urwin S, Parker MJ, Griffiths R. General versus spinal anaesthesia for hip fracture surgery: a meta-analysis of randomized trials. *Br J Anaesth* 2000; **84**: (in press)
6 Parker MJ, Prior GA, Myles J. 11-year results in 2,846 patients of the Peterborough Hip Fracture Project, reduced morbidity, mortality and hospital stay. *Acta Orthop Scand* 2000 (in press)

Drugs in Anaesthetic and Intensive Care Practice 8th edition

Editor—I and my co-authors are very grateful to you for your choice of reviewer. The author of a rival text can be relied on to spot any errors and is probably the best proofreader one could hope for. We are also grateful to Dr Calvey for the care and thoroughness with which he has undertaken the task

The multiple printing errors on Figure 8.1 should have been spotted by someone. Fortunately, as the first printing is on the point of selling out, we are ideally placed to correct this (and a few other errors) in a second printing. (This, incidentally, is at least a partial answer to Dr Calvey's rhetorical query as to whether this edition would prove as popular as previous ones.)

In one respect, however, I think Dr Calvey has been unfair. It is true that context-sensitive half-time is not mentioned in Chapter 1, but it is mentioned in the monographs on both propofol and remifentanil, the only anaesthetic drugs in which it is relevant. However, in case other readers look for the topic in vain, we have now introduced it into Chapter 1 as well, together with index references.

M. D. Vickers
Department of Anaesthesia and Intensive Care Medicine
University of Wales College of Medicine
Cardiff
UK

Editor—I note that Professor Vickers considers that one of the points made in my review is unfair. I accept that context-sensitive half-times are mentioned in the monographs on propofol and remifentanil–however, they are not discussed in the introductory chapter dealing with general pharmacology, which is the point I made in my review.

I also note that Professor Vickers and his colleagues propose to correct this and various other omissions in the forthcoming reprinting of their book.

T. N Calvey
University Department of Anaesthesia
Liverpool
UK

Temperature coefficients of the solubilities of inhaled anaesthetics

Editor—One of us recently had occasion to refer to our 1973 paper[1] on temperature coefficients of the solubilities of inhaled anaesthetics; he was horrified to find a typographical error in three of the equations as follows. Equations (1a) to (3a) are for *fractional* temperature coefficients and therefore the left-hand sides should all be $(d\lambda/dT)/\lambda$ (not just $d\lambda/dT$). In addition, the caption to the figure should have specified that the Ostwald solubility coefficients on the x-axis were all as at 37°C.

A copy of the submitted typescript shows that these errors of commission and omission were in the original, so the fault is entirely that of the authors; no blame attaches to the then editor. Fortunately, these were no more than typographical errors: the calculations and results were not affected by them.

We apologize to any readers who may have been misled and regret that one of the authors cannot join us in doing so: Alan Steward died suddenly in November 1999.

P. R. Alott
Information System Services
University of Exeter
Colchester
UK

V. Flook
Unimed Scientific Ltd
National Hyperbaric Centre
Aberdeen
UK

W. W. Mapleson
Department of Anaesthetics
University of Wales College of Medicine
Cardiff
UK

1 Alott PR, Steward A, Flook V, Mapleson WW. Variation with temperature of the solubilities of inhaled anaesthetics in water, oil and biological media. *Br J Anaesth* 1973; **45**: 294–300

Multiple authorship

Editor—Am I alone in questioning the need for multiple authorship of some of the short contributions and case reports published in the journal? I find it difficult to understand how an essay of two or three pages of text requires five, six or even seven authors and I wondered if the problem was unique to the *British Journal of Anaesthesia.* However, reference to my copies of the current issue of *Anaesthesia* and the *European Journal of Anaesthesiology* demonstrates an identical pattern. Moreover, examination of the general medical journals, *The Lancet* and the *British Medical Journal*, shows a similar trend.

It was not always so. As it happened, on a completely unrelated matter, I recently needed to consult the first paper I had ever had published in the *British Journal of Anaesthesia.* The year was 1953 but fortunately I had kept the relevant issue[1] and I took the opportunity to scan the contents list. It may come as a surprise to your younger readers, but of all the contributions only one had more than one author and that was a letter to the editor by two senior scientists based in Montreal who were seeking the assistance of the journal's readers in collecting data on stress. Otherwise, no paper had more than one author, the editorial was anonymous as were the book reviews and the case reports were under the title 'From the Morbidity Conference'. Two further contributions, an appreciation of A. Charles King and an obituary of R. J. Probyn-Williams were unsigned although initialled.

What has brought about this change? As I pondered over the possibilities, I had the good fortune to read a forceful and penetrating essay in *The Lancet* by Michael O'Donnell entitled 'Evidence based illiteracy: time to rescue the literature'[2] that put into words all my anxieties and doubts. In his opening sentence, Dr O'Donnell asserts and I quote 'That oft-evoked entity 'The literature' has been corrupted by a language created by people who write not to be read but to be cited.' His analysis was convincing and it was particularly heartening to discover that I was not alone in my anxieties about current trends in the medical journals.

Dr O'Donnell ends his paper with a proposal that has my full support. He suggests, and again I quote: 'If we could get the citation seekers out of our journals and into peer-reviewed electronic databases, we could rid ourselves of their vernacular and start to share our ideas in a clear, honest and interesting way.'

That of course needs the co-operation of editors, editorial boards and, perhaps most of all, the assessors who ensure that papers are suitable for publication. Will that co-operation be forthcoming? I would like to think so.

J P Payne
London
UK

1 Contents list. *Br J Anaesth* 1953; **25**: No. 2 April
2 O'Donnell M. Evidence-based literacy: time to rescue 'the literature'. *Lancet* 2000; **365**: 489–91

British Journal of Anaesthesia 84 (6): 831–2 (2000)

Book Reviews

Pharmacology and Physiology in Anesthetic Practice. R.K. Stoelting. Published by Lippincott-Raven, Philadelphia. Pp. 848; indexed; illustrated. Price US$99.00. ISBN 0-7817-1621-7.

This is the third edition of this well known American textbook. In the seven years since the publication of the second edition, there have been a significant number of new drugs introduced into clinical practice and advances in the understanding of a number of physiological processes. The stated aim of this textbook is to update the information to provide an in-depth but concise presentation, for students and practising anaesthetists, of aspects of physiology and pharmacology relevant to perioperative care.

The book consists of 770 pages divided into 58 chapters. Pharmacology accounts for 38 chapters (570 pages) and physiology for 20 (200 pages). This distribution generally reflects the strengths of the text where the pharmacology chapters address more precise subjects in detail and the physiology ones are dealt with more broadly. This is not a major criticism as it reflects both the greater volume and relevance of the advances in the two subjects to anaesthetic practice.

The pharmacology text covers the full spectrum of drugs used in anaesthesia and perioperative care. The sequence of chapters is in places a bit confused with, for example, a chapter on NSAIDs appearing between one on anticholinergics and one on sympathomimetics and then one on prostaglandins ten chapters on. The chapters are, on the whole, detailed and well structured with good use of figures and tables. Each chapter contains an extensive up-to-date list of references used in the text. It is nice to see an American text that uses an international set of references. The content of the chapters is generally accurate and current although there are inevitably some omissions, for example in the NSAIDs chapter there is no mention of COX 1 and 2.

The physiology text is, in my view, less comprehensive than the pharmacology one. The chapters do cover all the relevant topics and contain a considerable amount of information in a concise form. I found some areas to be too concise, for example *Pulmonary gas exchange and blood transport of gases* is dealt with in a chapter of just over eight pages and does not present the alveolar gas equation. The chapters are well illustrated with tables and figures, but the references are in the main to other physiology textbooks.

The book is well indexed and, as well as having a comprehensive subject index, it has a useful drug index for quick reference to specific drugs.

To use the old football catchphrase, this book is a game of two halves, with an excellent pharmacology 'half' and an adequate physiology one. I would have no hesitation in recommending this book to candidates preparing for the Primary FRCA examination with respect to the pharmacology content but would caution them that the physiology part would need some supplementation. As a reference text and source of teaching material this book would be a useful addition to a departmental library.

C. S. Reilly

Paediatric Anaesthesia, 2nd edition. E. Sumner and D. Hatch (eds). Published by Arnold, London. Pp 648; indexed; illustrated. Price £65. ISBN 0340719427.

At 10 pence per page, this book is very good value as a comprehensive textbook of modern paediatric anaesthesia which has been comprehensively revised since the first edition appeared some 10 years ago. Striking improvements in layout, content and indexing have turned this book into an authoritative and comprehensive international textbook of paediatric anaesthesia. The core authorship of 14 staff from Great Ormond Street, London is complemented by 19 others from North America, Australia and Europe. These international perspectives have greatly enhanced the book. Twenty three chapters are grouped into those covering the basic core curriculum of modern paediatric anaesthesia (12 chapters); those covering sub-specialty areas (seven chapters); chapters covering unusual conditions in paediatric anaesthesia; anaesthesia and sedation outside the operating room; resuscitation, and organization of paediatric anaesthesia. The outstanding chapters for me as both a paediatric anaesthetist and intensivist were those on cardiac anaesthesia, airway obstruction, day-stay surgery, unusual conditions and anaesthesia/sedation outside the operating room. There is good practical advice throughout the book, for example in the chapter on pain management and in the appendices. There is plenty of evidence of the impact on paediatric anaesthesia practice of drug developments such as sevoflurane, and of new techniques such as the use of the laryngeal mask airway. The line drawings are clear and useful throughout and some outstanding black and white photographs are included in the chapter on airway obstruction. The excellent layout of the text is complemented by clear and helpful tables, summary boxes and algorithms.

All in all, this book is a 'must-have' for every trainee in anaesthesia. It is a useful refresher for consultants and should be a core text for every department delivering anaesthesia services to children. The book will also be of great interest and benefit to operating department personnel, ward nursing staff and paediatric medical staff from all the Royal Colleges! I cannot commend this book highly enough.

N. S. Morton

Irwin and Rippe's Intensive Care Medicine, 4th edition. Published by Lippincott-Raven, Philadelphia. Pp. 2518, 2 volumes; indexed. Price US$225. ISBN 0-7817-14257.

If you were a specialist in intensive care in the USA or Australia, *Irwin and Rippe's Intensive Care Medicine* would be familiar as a core text. The fourth edition comes three years after the third edition and some 15 years since the first edition was published. This represents a genuine attempt by editors and publishers to keep abreast of the rapid changes in this speciality. At its inception it was obviously a medical intensive care textbook, its editors' roots being in pulmonary medicine and cardiology. Gradually through each edition the balance between surgical and medical intensive care has improved aided by a third editor, Cerra, a Professor of Surgery. However, the book has kept its original title (Irwin and Rippe's) and many chapters are clearly written predominantly by physicians and not 'intensivists'.

Two volumes, 28 sections, 227 chapters and over 2500 pages, it is truly an encyclopaedic tome. However, it falls into the usual traps we would perceive in a book of this size. For the editors it is a gargantuan task to put together a book on this scale. Twenty-four section editors and a total of 331 contributors leads to obvious problems with quality control and duplication of information across the chapters. Although the editors claim that 'every contributor has been challenged to add new state of the art information and discard outdated less clinically relevant data', there are a paucity of references after 1996. As with many American textbooks, it appears parochial from the European perspective. If one scans the list of contributors, of 331 only seven come from outside the

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USA, over half come from hospitals in the same States as the editors and this includes over one third from Massachusetts. Are Worcester and Boston, Massachusetts truly the world centres of excellence in intensive care?

The actual layout of the book is clear and methodical, many chapters are brilliant (too many to list), all are comprehensive. Each chapter is extensively referenced. The first section on procedures and techniques is useful particularly for trainees (30 chapters), but percutaneous tracheostomy and gastric tonometry could have received more critical appraisal as opposed to being minor inclusions. Sections 2–5 and 7 cover conditions encountered under organ system headings. Section 6 is on infectious disease problems in intensive care, but there is little emphasis on antibiotic resistance in the critically ill patient.

Section 10 (38 chapters) is almost a textbook in its own right: Pharmacology, Overdoses and Poisonings. It is one of the most detailed attempts to consolidate this topic I have ever read. Again it is a little out of date; ecstasy and selective serotonin reuptake inhibitors do not really appear. Sections 11 and 12, Surgical problems and Shock/Trauma are good, but septic shock gets about 12 pages out of 2500 (what intensive care journal can you pick up these days without some editorial or research into pathophysiology of septic shock). The final sections on Nutrition, Psychiatric problems and Moral/Ethical issues strongly consolidate the completeness of this textbook.

The two volumes are really impressive in their content and I struggled to find either a mainstream subject or peripheral topic that is not documented, explained and resolved within their pages. This book would sit well in a library, but probably not on a personal bookshelf. Anyone working in intensive care or preparing for the Diploma should have access to this sort of book, but before buying, would do well to view two others and assess which style suits best: *Principles of Critical Care*, 2nd edition 1998, Jesse Hall, a much less parochial American textbook with an extensive list of well known authors in intensive care medicine; and *Oxford Textbook of Critical Care*, 1999, an international textbook with a unique style, which highlights key messages and the most recent relevant references.

Textbooks of this size will never be as up-to-date as a monthly journal such as *Critical Care Medicine*, but within intensive care there are some evidence based issues of the late 1990s which I would have liked to have seen given more emphasis in *Irwin and Rippe's Intensive Care Medicine*. Many people will appreciate this textbook. It is authoritative and detailed. I think there has been a lost opportunity to be the intensive care textbook for the new millennium; its style is 'all inclusive', though unimaginative and predictable. A final comment for the publishers would have to be, where on earth did the paper come from!

T. H. Gould

Careers in Anesthesiology. Autobiographical Memoirs Volume III. B.R. Fink and K.E. McGoldrick (eds). Published by Wood Library-Museum of Anesthesiology, Park Ridge, Illinois. Pp. 214; illustrated. Price US$35. ISBN 1-889595-02-0.

When the first volume of this series appeared in 1997, I had the privilege of reviewing it.[1] I commented then that further volumes would do well to reach the standards of the first one and that perhaps there was a danger of them becoming 'more of the same'. To some extent, this had occurred. All the authors are writing of the era in which anaesthesia developed from a skilled craft to a precise science. Consequently, with a few exceptions, their life stories do not differ greatly.

Volume III includes two non-American authors, Stanley Feldman from Britain and Carlos Parsloe from Brazil and both make valuable contributions. Parsloe's capacity for almost total recall, both for the important and the trivial, makes entertaining reading. The American writers are Ephraim S. Siker, John E. Steinhaus and Peter M. Winter. Although they offer different emphases I did not feel that they added greatly to the picture of American anesthesiology I had derived from the earlier volumes.

Obviously, the most interesting essays are from those writers who not only describe their lives but also attempt to evaluate the significance of the events they lived through and to which they contributed. Papper did this outstandingly well in Volume I, but in this one only Feldman and to a very small extent, Winter and Steinhaus, do so. Their conclusions are different. Winter limits his analysis to the topic, important though it is, of the qualities of leadership demanded of a head of department. Steinhaus looks into the future and sees it rosy, as least as far as the technological aspects of anaesthesia are concerned. Feldman, however, is more perceptive and he comes to the same conclusion as did Papper in Volume I in sadly regretting current trends. Papper was desperately concerned about the future of medicine in America, seeing anesthesiology as the first casualty in the latest revolution where medical practice is driven entirely by economics and cost containment.[2] Feldman goes even further, pointing out that in the past the anaesthetist was a physician, a learned doctor, a savant who applied his knowledge to look after a patient under anaesthesia, whilst today he is merely a technician employed to give anaesthetic A for condition B. This trend seems to be world-wide, perhaps a reflection of the anti-professional attitudes so current in today's society. Both Feldman and Papper regard themselves as being fortunate to have belonged to the lucky generation and those of us of that same generation will share their regrets and their anxieties.

The Editor's Note describes the series as 'a new experiment in living history ... autobiographical panoramas of the protracted revolution which overtook anesthetic practice in the second half of the twentieth century'. The written word can hardly be regarded as a new medium and in this technological era one might reflect on whether the essay published in book form is still the best way to record memoirs. The story may be well told, but the personality of the author comes across less well. Film, video, even audiotaping shows this much better. Furthermore, the written essay includes only what the writer chooses to reveal, whereas a skilled interviewer may probe aspects which the subject himself may have overlooked, whilst the interplay between the two may result in far-reaching discussions that can become the most important part of the whole communication. On the other hand, film and video are less user-friendly; text can easily be scanned by the reader to pick up what interests him, but scanning video is much less easy, is more time-consuming and cannot be done on the train! Furthermore, the written word survives for centuries, whilst we do not yet know how long electronic media can be made to last.

The Wood Library-Museum is therefore making an important contribution. Other institutions possess collections of memoirs in various media, whilst the Association of Anaesthetists of Great Britain and Ireland is currently sponsoring a series of videotaped interviews of senior anaesthetists. The relative shortness of the history of scientific anaesthesia makes it particularly suitable for the building up of a comprehensive archive and there is advantage in having a variety of material available for the reference of present and future historians. The inclusion of non-American authors is to be welcomed. It gives a more extensive view, for right from its beginnings anaesthesia developed differently throughout the world.

The production is of high quality and happily the numerous misprints which marred previous volumes have been eliminated, whilst the inclusion of an index of abbreviations is helpful.

A. K. Adams

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[1] Adams AK. Book Review. *J Med Biog* 1998; **6**: 123–4

[2] Papper EM The palate of my mind. In: Fink BR (ed.). *Careers in Anesthesiology. Autobiographical Memoirs. Volume I.* Park Ridge, Illinois. Wood Library-Museum of Anesthesiology, 1997; 214–7

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Erratum

Hot air or full steam ahead? An empirical pharmacokinetic model of potent inhalational agents (BJA 2000; 84: 429–33)

The last sentence of the first paragraph (page 429) was printed incorrectly. The sentence should read. So why do the pharmacokinetics of volatile anaesthetics at all?

The publishers apologize for this error that arose during the copyediting process.

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Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Illustrations

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The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, methods, results and conclusions, and normally should

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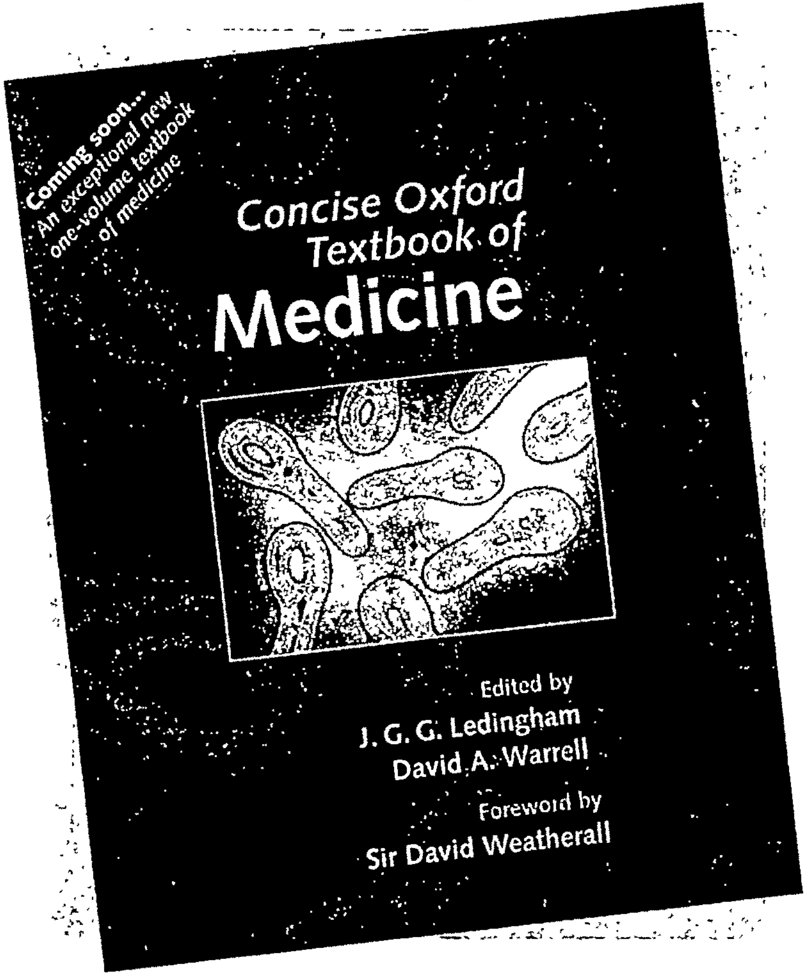

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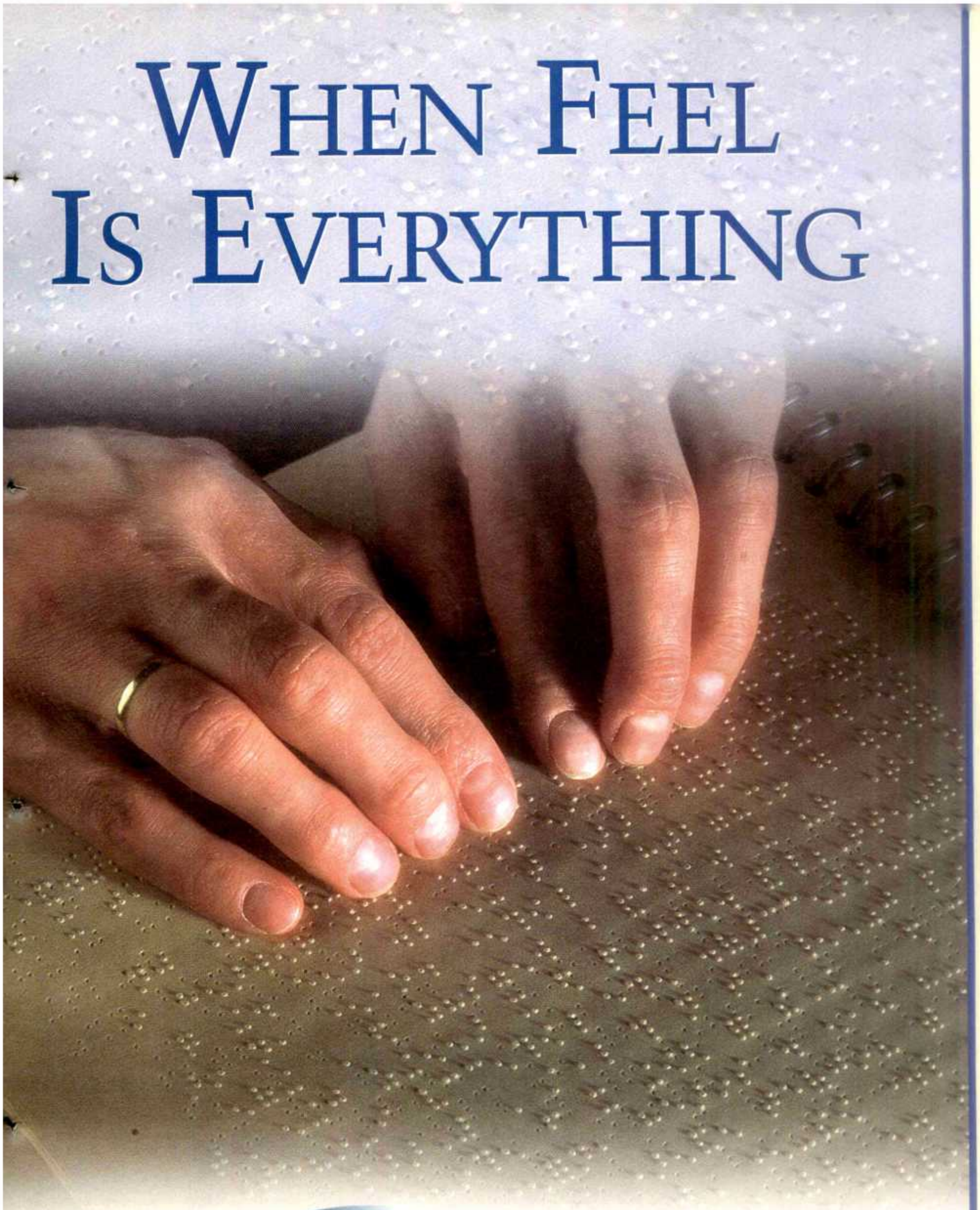

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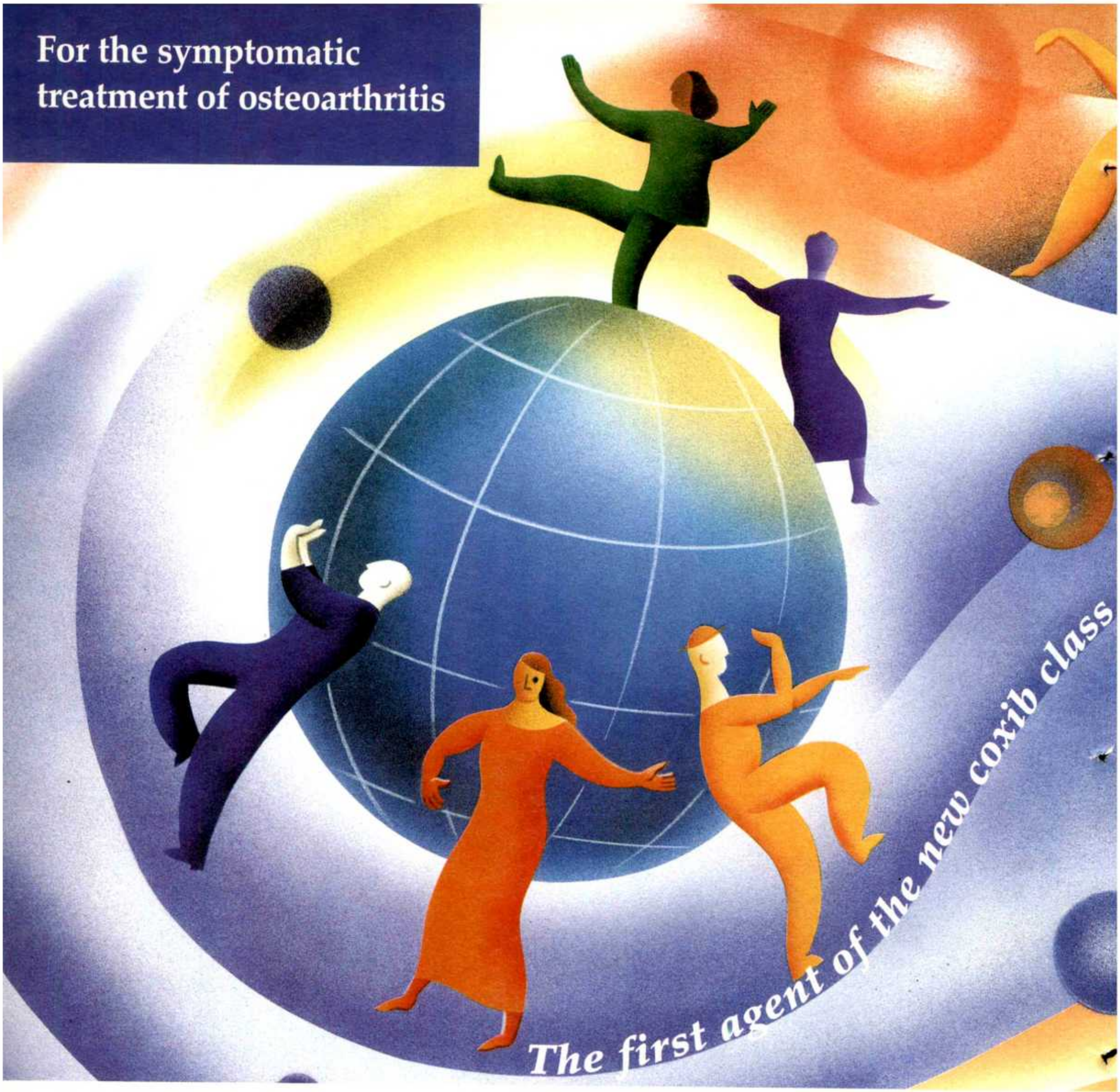
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The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded.

Elderly: Exercise care when increasing the dose from 12.5 mg to 25 mg.

Hepatic insufficiency: In mild hepatic insufficiency, do not exceed 12.5 mg once-daily.

Children: Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib.

Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension.

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

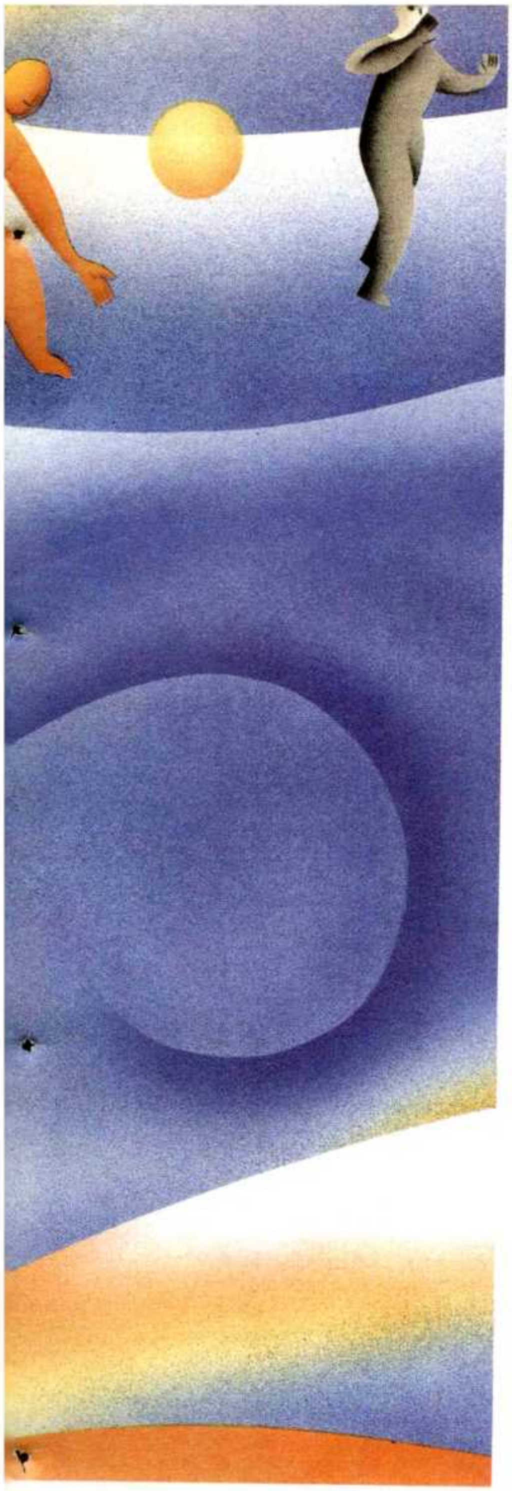
Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib. Rofecoxib may mask fever.

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone.This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of



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rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with rofecoxib for one year or longer.

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

PACKAGE QUANTITIES AND BASIC NHS COST

Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58.

Oral Suspension 12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12.

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References:

1. Ehrich EW, Dallob A, De Lepeleire I et al. Characterization of rofecoxib as a cyclo-oxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999; 65(3):336-347.
2. Data on file, Merck Sharp & Dohme Limited.
3. Langman MJ, Jensen DM, Watson DJ et al. Adverse upper gastro-intestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;282(20):1929-1933.

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Uses: As an adjunct to general anaesthesia to facilitate endotracheal intubation during routine and rapid sequence induction, to provide skeletal muscle relaxation, during surgery. Esmeron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation.
Dosage and administration: Esmeron is administered intravenously as a bolus or as an infusion. See Summary of Product Characteristics for compatibilities.
Dosage is individualized taking into account method of anaesthesia, duration of surgery, possible interactions with other drugs and the patient's condition. Routine use of appropriate neuromuscular monitoring technique is recommended.
In adults: For short to long lasting surgical procedures:
Intubation: 0.6 mg / kg, Rapid sequence induction 1.0mg/kg,
Maintenance dose: 0.15 mg/kg, (reduce to 0.075mg - 0.1mg/kg for Long-term inhalational anaesthesia).
Continuous infusion: Loading dose 0.6 mg/kg, then infusion rate 0.3 - 0.6 mg/kg/hour or under inhalational anaesthesia 0.3 - 0.4mg/kg/hr. Continuous monitoring of block is essential.
(See Summary of Product Characteristics for advice for intensive care procedures, children, elderly, cirrhotic and overweight patients).
Contraindications Previous anaphylactic reactions to rocuronium or the bromide ion.
Precautions and warnings: Use under the supervision of experienced clinicians familiar with neuromuscular monitoring techniques. Ventilation is mandatory until adequate spontaneous respiration is restored. Dose levels above 0.9 mg/kg may increase heart rate which could counteract bradycardia produced by other anaesthetic agents or vagal stimulation. Hepatic and/or biliary tract disease, renal failure, prolonged circulation time and neuromuscular disease hypothermia and obesity may influence the effects of Esmeron. Severe electrolyte disturbances, altered blood pH or dehydration should be corrected when possible. Clinicians should be aware of the signs and symptoms of malignant hyperthermia
Effect on ability to drive or use machines: Using potentially dangerous machinery or driving are not recommended within 24 hours of full recovery.
Use in pregnancy and lactation: Esmeron should be given to pregnant or lactating women only when the benefits outweigh the risks. Dose in Caesarean section: 0.6mg/kg.
Side effects: Anaphylactic reactions are very rarely seen. No clinically significant tachycardia, hypotension or other clinical signs of histamine release have been reported.
Interactions: Other drugs may influence the effects of non-depolarizing NMBA's, including anaesthetics, other NMBA's, antibiotics and suxamethonium, diuretics, (-adrenergic blocking agents. See Summary of Product Characteristics for details.
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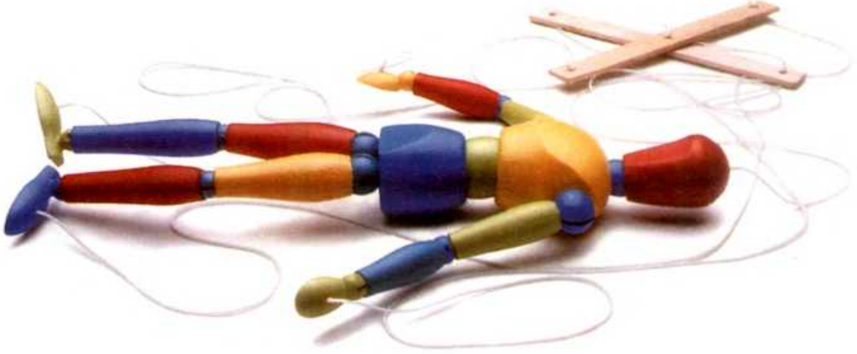

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1. Puhringer et al. Anesth. Analg. 1992; 75: 37 - 40 **2.** Foldes et al. Exc Med Ams. 1990: 171 - 181 **3.** Sparr et al. Eur J Anaesth. 1994: 11(9): 63 - 65 **4.** Naguib et al. Br J Anaesth. 1995; 75: 588 - 592

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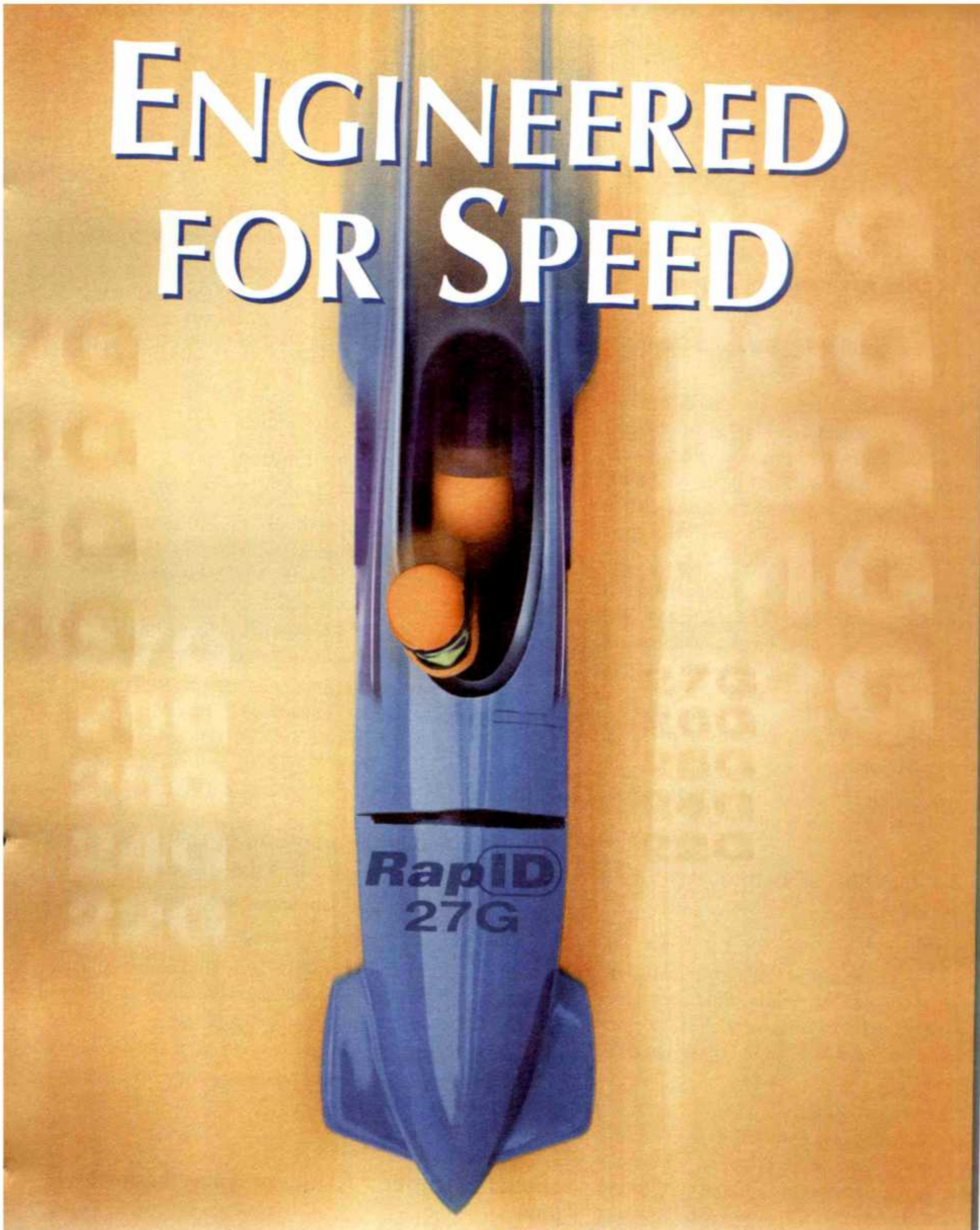

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Bradford, UK, 2000, September 15, 2000 and October 27, 2000

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Of interest to all those involved in the management and investigation of patients with back pain and sciatica as well as those involved with central neural blocks. Numbers of delegates strictly limited. Lunch will be provided.

For further information please contact:

Dr Jonathan Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford, BD9 6RJ.

Tel: +44 1274 364271/364253; Fax: +44 1274 366811; E-mail: merit.centre@mail.bradh-tr/northy.nhs.uk

Therapeutic Applications of Leukocyte Filtration

London, July 7, 2000

The Hammersmith Hospital, Imperial College, London, UK, is pleased to stage a one-day workshop. This prestigious meeting is being organized by Professor Ken Taylor and Dr Terry Gourlay who have invited a guest panel of international speakers.

Topics presented include: Angioplasty Therapy for Acute Myocardial Infarction with Leukocyte Filtration; Filtration of Malignant Cells using Leukocyte Filtration on Cardiopulmonary Bypass; Leucofiltration of Cell Salvaged Blood; Techniques and Timing of Systemic Leukocyte Filtration on Cardiopulmonary Bypass; Leukocyte Depletion in Vascular Surgery; Leukocyte Tactics and Improved Patient Outcome After Extracorporeal Circulation; Leukocyte Filtration in Paediatric Cardiac Surgery; Systemic Leukocyte Filtration during Cardiopulmonary Bypass; Effects of Leukocyte Filtration of Blood Transfusion on Postoperative Complications; The Therapeutic Benefit of Depleting Blood Polymorthonuclear Cells from Patients with SIRS; Role of Leukodepletion in SIRS.

Abstracts are invited for poster presentations at this workshop. Abstract forms are available from the conference centre (address below). Prizes will be awarded to the best three abstracts.

Further details and registration forms are available from:

Jean Bryant, Manager, Wolfson Conference Centre, Imperial College of Science, Technology and Medicine, Hammersmith Hospital, Du Cane Road, London W12 ONN, UK.

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Edinburgh, August, 23–25, 2000

Organized by the Department of Anaesthetics, Royal Infirmary of Edinburgh, to coincide with the 2000 Edinburgh International Festival of the Arts. The 3-day programme consists of lectures and discussion on current topics in anaesthesia. The lecturers are from all parts of the United Kingdom and represent leading opinions in their field.

For further information: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW. Tel: +44 131 536 3652; Fax: +44 131 536 3672; E-mail: anaes@ed.ac.uk

The Fifth Annual Symposium of the Association for Low Flow Anaesthesia

Ulm/Neu-Ulm/Germany, September 8–9, 2000

For further information, please contact:

Priv. Doz. Dr Uwe Schirmer, Priv. Doz. Dr Thomas Marx, Department of Cardiac Anaesthesia, University of Ulm, Steinhövelstr. 9, D-89075 Ulm, Germany.

Tel: +49 731 5021521; Fax: +49 731 5026757; e-mail: alfa2000@gmx.net; congress homepage http://www.uni-ulm.de/alfa2000.

Annual Scientific Meeting in Anaesthesiology 2000

Hong Kong, September 8–10, 2000

We have great pleasure to advise you that the captioned Meeting will be held on 8–10 September 2000 at the Sheraton Hong Kong Hotel and Towers.

Provisional Scientific Programme. Airway Workshop (Prof. David Chung); Regional Anatomy, Workshop for Regional Blocks (Prof. Phillip Bridenbaugh); Evidence Based Medicine Workshop (Dr. Florence Yap and Dr. Gavin Joynt); Keynote Lectures: Perioperative Medicine – International Perspective (Chairman: Dr T. W. Lee) (Prof. Phillip Bridenbaugh); (Prof. Mathieu Gielen); (Dr Neil MacIntyre)

Panel Discussion: Medical Liability *vs* Litigation (Chair-

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man: Dr T. W. Lee) (Mr Douglas Jones and Mr Chris Howse). Debates (Chairman: Dr C. T. Hung) (Prof. Michael Irwin and Prof. Warwick Ngan Kee *vs* Dr Phoebe Mainland and Dr Eddie Cheam); ICU Workshop Weaning from Ventilator (Dr Neil MacIntyre).

Keynote lectures: Perioperative Medicine—International Perspective Chairman: Dr T. W. Lee. The Road Ahead—Anaesthesiologist as Perioperative Physician (Prof. Phillip Bridenbaugh); Lung Protective Ventilatory Strategies (Dr Neil MacIntyre); Perioperative Pain Management—Comfort, Care and Cure (Prof. Mathieu Gielen).

Plenary session I. Test No Test? (Prof. Michael Irwin); Premedication—In or Out (Dr Jeffrey Kua); Perioperative Haemodynamic Goals (Dr Gavin Joynt).

Plenary session II. Preemptive Analgesia: Fact or Fallacy (Prof. Phillip Bridenbaugh); Anaesthetic Techniques—A Look into the Future (Prof Tony Gin); Continuous Spinal Anaesthesia—Is There a Role in Anaesthesia and Postoperative Analgesia (Prof. Mathieu Gielen).

Plenary session III. Chairman: Prof. Tom Buckley. Evaluation and Management of Postoperative Respiratory Insufficiency (Dr Neil MacIntyre); Acid-Base Secrets (Dr Ian Tan); Post-Anaesthetic Care—How Far Should We Go? (Dr C. T. Hung).

Refresher Course topics include: New Analgesic Agents (Dr S. L. Tsui); Anaesthesia for Cerebral Aneurysm Surgery (Dr Sathasivam Anandaciva); Advances in Clinical Measurement (Dr James Derrick); Paediatric Anaesthetic Emergencies (Prof. Cindy Aun); Day Case Anaesthesia (Dr Gwen Fok); Physiology of Consciousness (Prof. Michael Irwin); Spinal Anaesthesia for Day Surgery (Prof. Mathieu Gielen); Clinical Pharmacokinetics (Prof. Tony Gin); Anaesthesia for High-Risk Parturients (Prof. Warwick Ngan Kee); Physiology of Pregnancy (Dr K. K. Lam); Anaesthesia for Thoracic Aneurysms (Dr Das); and TEE (Dr Peter Hiong)

For further information please contact Ms Melissa Leung of the Federation of Medical Societies of Hong Kong. Tel: (852) 2527 8898; Fax: (852) 2866 7530

XIX Annual Congress of the European Society of Regional Anaesthesia Joint Annual Congress with EuroPain 8th European Conference on Pain Research

Rome, Italy, September 20–23, 2000

The congress will be held in the Sheraton Hotel.

Abstract deadline is June 1, 2000.

For further information, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 5643; Fax: +032 2 346 5435;
E-mail: dionne@options.com.cy

Collaborative Conference between Bournemouth University and Salisbury Health Care NHS Trust

Salisbury, UK, September 21, 2000

Day Surgery Conference at Salisbury District Hospital.

For further information please contact: Sam Williams, Administrative Assistant, IHCS, Bournemouth University, Royal London House, Christchurch Road, Bournemouth, BH1 3LT. Tel: +44 (0)1202 504196

Refresher Course in Anaesthesiology

Durban, South Africa, September 22–23, 2000

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–27, 2000

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Surfactant 2000

From Trier to Basle September 23–29, 2000

This is an international floating congress on the rivers Mosel and Rhine. All aspects of surfactant (basic science/clinical applications) will be addressed.

For further information, please contact:

Dr B. Lachmann, Department of Anesthesiology, Erasmus University Rotterdam, Postbox 1738, 3000 DR Rotterdam, The Netherlands.
Web site: http://www.floating-congress.vet.uu.nl

13th Annual Congress of the European Society of Intensive Care Medicine

Rome, Italy, October 1–4, 2000

For further information, please contact:

ESICM Congress Secretariat, 40 Avenue Joseph Wybran, B-1070 Brussels, Belgium.

Tel: + 32 2 559 0355; Fax: +32 2 527 0062; E-mail: public@esicm.org; Internet http://www.esicm.org

Dingle 2000 – Current Controversies in Anaesthesia and Perioperative Medicine

Dingle, County Kerry, Ireland, October 4–8, 2000

University College London Hospitals Centre for Anaesthesia announce a call for abstracts: there is an opportunity to submit work for poster presentation and selected finalists will be invited to give an oral presentation (prizes totalling £1000). Any research is acceptable provided it has not been published in any peer reviewed journal by the abstract deadline of 30 June 2000.

For further abstract and meeting registration details please contact:

Dr Monty Mythen, Centre for Anaesthesia, Room 103, 1st Floor Crosspiece, Middlesex Hospital, Mortimer Street, London, W1N 8AA, UK.

Tel: +44 20 7380 9477; Fax: +44 20 7580 6423;
E-mail: uch.acru@btinternet.com

European Academy of Anaesthesiology European Diploma in Anaesthesiology and Intensive Care

Part I (MCQ), October 7, 2000

(Endorsed by the European Board of Anaesthesiology (EBA) of the Union of European Medical Specialists (UEMS)

This examination will be held in English, French, German, Italian and Spanish in Athens, Barcelona, Berne, Budapest, Cluj-Napoca, Göttingen, Liège, Ljubjlana, London, Lund, Moscow, Oslo, Paris, Poznan, Riga, Rome, Tel Aviv, Uppsala and Vienna.

Regulations and application forms are available from:

Examinations Manager, European Academy of Anaesthesiology, London House, 243 Lower Mortlake Road, Richmond, Surrey TW9 2LS, UK.
Tel: +44 (0)208 940 6240; Fax: +44 (0)208 940 6262; E-mail: DEAA@compuserve.com; Home page: http://eaa-web.eu.org

The closing date for receipt of applications is May 31, 2000 (fee: £170)

Applications received after the closing date or unaccompanied by the full fee cannot be accepted and will be returned.

Wood Library-Museum's Quadrennial Laureate of the History of Anesthesia Prize

Members of the Editorial team of the *BJA* are pleased to announce that, Dr Thomas B. Boulton (UK) and Dr Norman A. Bergman (USA) are to be awarded the Wood Library – Museum's quadrennial Laureate of the History of Anesthesia Prize at the annual meeting of the American Society of Anesthesiologists in October 2000, in San Francisco.

We offer our hearty congratulations to Dr Boulton, and to the family of Dr Bergman, who unfortunately died recently.

Haemostasis and Transfusion—Perioperative Management in Elderly Patients

Graz, Austria, October 27 and 28, 2000

This symposium has been organized by the Department of Anaesthesiology and Intensive Care Medicine, University of Graz and Department of Anaesthesiology, University of Munich.

The preliminary programme includes: haemostasis and transfusion, and perioperative management in elderly patients.

For further information contact: M. Neuray/G. Taucher, Department of Anaesthesiology and Intensive Care Medicine, LKH-Universitätskinikum Graz, Auenbruggerplatz 29, A-8036 Graz, Austria. Tel: +43 316 385 3027; Fax: +43 316 385 4664; E-mail: haemostasis@kfunigraz.ac.at. www.kfunigraz.ac.at/uanwww/haemostasis.htm

St Bartholomew's Hospital Choral Society

Royal Albert Hall, London, UK, November 21, 2000

St Bartholomew's Hospital Choral Society celebrates the millennium and their 35th anniversary with the Royal Medical Benevolent Fund as their chosen Charity for their season 2000/2001.

Mahler's Symphony No. 8 'Symphony of a Thousand' with the Royal Philharmonic Orchestra, Royal Albert Hall, 21 November 2000.

It needs a *really* big choir, splendid orchestra, fine soloists and conductor. Six hundred singers are needed for this monumental work.

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The Royal Medical Benevolent Fund, 24 King's Road, Wimbledon, London SW19 8QN.

Tel: +44 20 8540 9194; Fax: +44 20 8542 0494;
E-mail: rm.bf@virgin.net

11th Congress, Western Pacific Association of Critical Care Medicine

Singapore November 29–December 3, 2000

This meeting will take place at the Westin Stamford and Westin Plaza, Singapore and is organized by the Society of Intensive Care Medicine (Singapore).

For further information, please contact:

11th WPACCM Congress Secretariat, Academy of Medicine, Singapore College of Medicine, Building 16, College Road, #01-01, Singapore 169854.
Fax: +65 225 5155; E-mail: monicaw@pacific.net.sg

19th Annual Symposium Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

San Juan, Puerto Rico, January 13–20, 2001

Free Papers will be accepted for oral and poster presentation in four categories: (i) monitoring; (ii) new pharmacological agents; (iii) interesting case reports; (iv) cardiopulmonary bypass technology. Abstracts forms are available upon request. The deadline for submission is November 1, 2000. Tuition will not be waived. Brochure available in June 2000.

For information and abstract forms contact: Helen Phillips, Box 1010, Mt. Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029-6574, USA.

Tel: +1 212 241 7630; Fax: +1 212 426 2009; E-mail: helen_phillips@smtplink.mssm.edu

2nd International Conference on Pain Control and Regional Anaesthesia

Jaipur, India, February, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA 4th Workshop ‘Neural Blockades on Cadavers’

(European Society of Regional Anaesthesia)

Innsbruk, Austria, February 22–24, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESA 8th Annual Congress

(European Society of Anaesthesiologists)
Gothenburg, Sweden, April 10, 2001

Abstracts deadline: December 1, 2000

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

Anita Akabogy, Congress Department, MCN Medizinische Congress-organisation Nürnberg AG, Zerzabelshofstrasse 29, 90478 Nuernberg, Germany.

Tel: +49 911 393 16 10; Fax: +49 911 393 16 55; E-mail: akabogu@mcn-nuernberg.de; www: http://www. mcn-nuernberg.de

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg, June 13–16, 2001

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

Awareness during Anesthesia—The 2000 *Anesthesiology* Journal-sponsored Symposium at the ASA Meeting

San Francisco, California, October 17, 2000, 9:00–12:30

The moderators will be Alex S. Evers MD (Washington University, St Louis) and Richard B. Weiskopf MD (University of California, San Francisco)

Awareness during anaesthesia is a potential problem of concern to clinicians and the public. There are clear cases of patients having been unintentionally awake during anesthesia and surgery and other cases for which 'awareness' was not as clearly delineated. 'Awareness' during anaesthesia and surgery can result in 'post-traumatic stress syndrome'.

This symposium will include invited speakers and a discussion session, as well as an opportunity to view selected abstracts. Abstracts in the following areas are considered appropriate for submission:

(i) epidemiology of 'awareness' during anaesthesia,
(ii) monitoring of depth of anaesthesia,
(iii) prevention of awareness during anaesthesia,
(iv) treatment of syndromes resulting from awareness during anaesthesia.

Abstracts should be submitted via the regular Annual Meeting procedures by April 1, 2000. *Online submission is available.* Abstracts requesting consideration for presentation at this symposium will undergo an additional review in addition to the standard ASA abstract review process. If you would specifically like your abstract considered for inclusion in the symposium, please check the special box that can be found on the cover letter/form which must accompany your submission. If you need abstract submission materials, please contact the American Society of Anesthesiologists:

American Society of Anesthesiologists, 520 N. Northwest Highway, Park Ridge, IL 60068–2573, USA.
Tel: +1 847 825 5586; Fax: +1 847 825 1692;
E-mail: mail@ASAhq.org Web site: http://www.asahq.org

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Leonard Firestone, M.D.
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Fax: (412) 648-1887
E-mail: firestone@anes.upmc.edu

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330-336 Gray's Inn Road, London WC1X 8EE
Telephone: 020 7915 1514/92 Fax: 020 7837 9279
e-mail: o.fender@ucl.ac.uk

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2 PEDIATRIC ANESTHESIOLOGISTS

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The Department of Pediatric Anesthesia is seeking an anesthesiologist with training and experience in pediatric anesthesia to join a 15 member department delivering care in the pediatric tertiary referral centre for British Columbia.

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In accordance with Canadian immigration requirements, priority will be given to Canadian Citizens and permanent residents of Canada. The Children's & Women's Health Centre of British Columbia hires on the basis of merit and is committed to employment equity. We encourage all qualified persons to apply.

Review of applications will commence immediately. Interested applicants should submit a letter and their curriculum vitae including a list of three references **by August 30, 2000** to:

Dr. Derek Blackstock
Head of Anesthesia
British Columbia's Children's Hospital
4480 Oak Street, room 1L2
Vancouver, BC V6H 3V4
Telephone: (604) 875-2711 Fax: (604) 875-3221
E-mail: dblackstock@cw.bc.ca

Visit our website at www.cw.bc.ca

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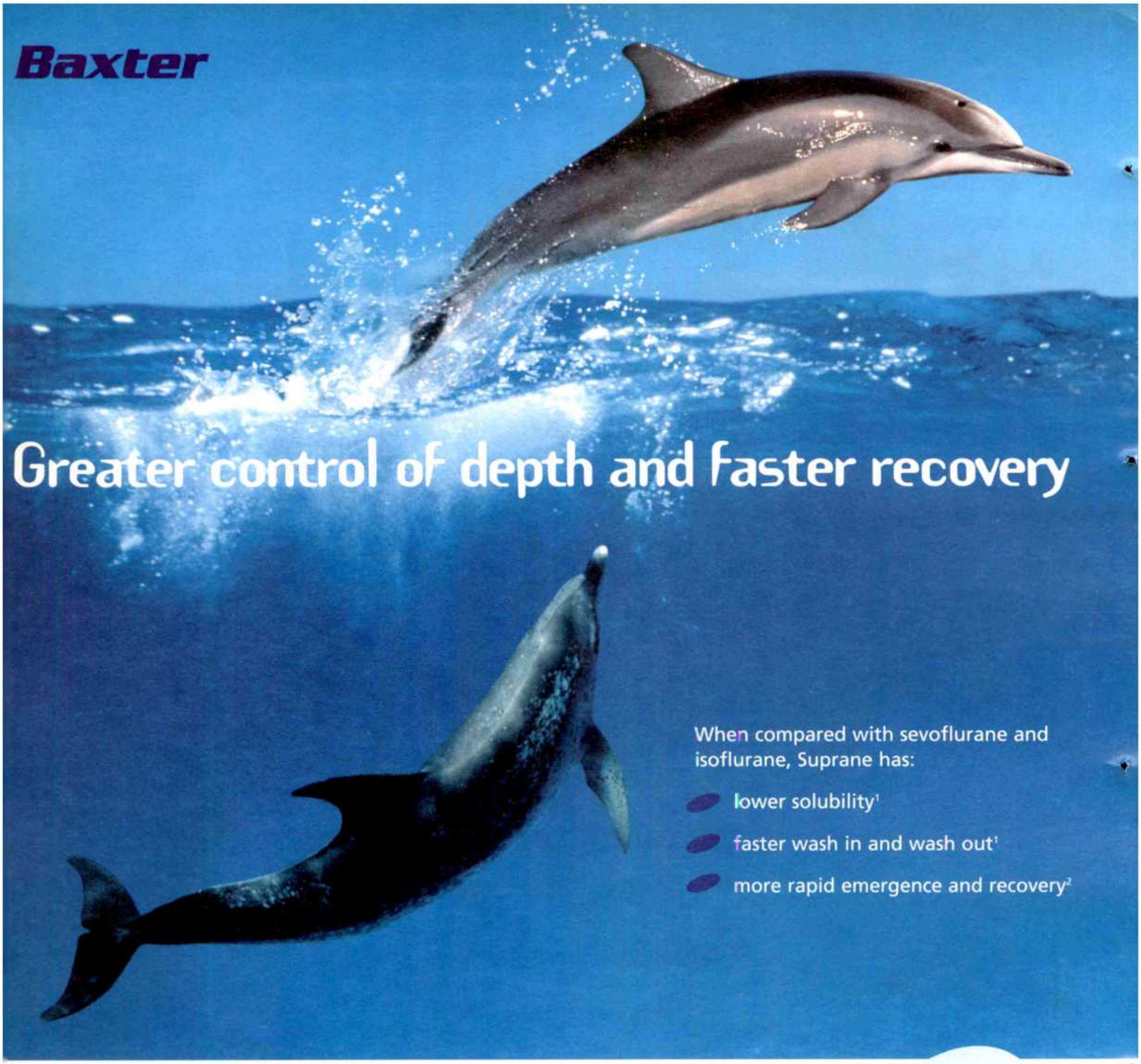
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Date of preparation: December 1999.
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References: 1. Eger E I. Anesth. Review. 1993;**20**:87-92.
2. Dupont I et al. Br J Anaesth. 1999;**82**:355-359.

Baxter Healthcare Ltd., Wallingford Road, Compton,
Nr. Newbury, Berkshire. RG20 7QW. Tel: 01635 206000

BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

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Editorial

Endocrine and metabolic disorders in anaesthesia and intensive care

'We do not expect people to be deeply moved by what is not unusual.'
G. Eliot, *Middlemarch* 1871–2

There are certain clinical challenges that we meet only occasionally in anaesthetic practice. They may be difficult to manage: more conscious effort is required and one needs to refer to a readily available text. Endocrine disorders fall into this category. Some are not uncommon in the general population such as insulin-dependent diabetes mellitus or thyroid disease, but others occur much less frequently, such as carcinoid syndrome or Cushing's disease.

Anaesthesia for patients with endocrine disorders was the subject of a symposium held by The Royal College of Anaesthetists in London in March 1999. It has also, on at least two occasions, been the subject of one of the popular symposia held at the Association of Anaesthetists of Great Britain and Ireland headquarters in Bedford Square, London. We thought it appropriate to invite selected speakers from these symposia to submit didactic reviews for publication on their area of interest. We have added to these topics for completeness, with reviews of the anaesthetic aspects of such rare metabolic disorders as porphyria by international experts on the subject,[1] and an update on malignant hyperthermia.[2] We have also considered related topics such as the stress response to surgery[3] and the perioperative challenges of the morbidly obese patient.[4]

Understanding the endocrine response to anaesthesia and surgery is fundamental to successful management of all patients undergoing a major operation. Desborough describes this rapidly developing area succinctly and with considerable clarity.[3] Our knowledge of cytokines and other acute phase proteins which trigger the stress response is increasing rapidly and anaesthetists need to be regularly updated on this topic. Anaesthetists dread the management of a morbidly obese patient presenting for major surgery. Will the patient fit on the operating table; will they breathe adequately postoperatively; and who will manage their inevitable postoperative problems? These points are addressed by Adams and Murphy,[4] who instil us with the confidence to face this particular challenge in the future.

Most anaesthetists in adult practice will occasionally have to manage patients presenting for thyroid surgery. Always a potentially challenging area because of the risk of a difficult intubation, anaesthetic techniques for management of the airway in the presence of an enlarged thyroid gland have developed alongside fibreoptic intubation and the increasing range of airways and laryngoscopes that have become available. These are discussed in detail by Farling.[5] Similar anaesthetic techniques are required for parathyroid surgery, yet the hormonal and biochemical problems which these patients present are very different. Knowledge of the physiology of calcium regulation has increased significantly. It is a complex area, often unfamiliar to anaesthetists, which is ably described by Mihai and Farndon.[6] The anaesthetic problems which may be encountered in patients with hyperparathyroidism are also detailed.

Perhaps the endocrine disorder that all anaesthetists consider to be the greatest challenge is phaeochromocytoma, often known as 'the great mimic'. Such patients can present unexpectedly during anaesthesia, or for planned surgical excision. Thorough preoperative preparation is pivotal to successful intraoperative management. This challenge is detailed by Prys-Roberts,[7] together with an account of his extensive experience in the management of these patients over many years.

Anaesthesia for patients with pituitary disease is a highly specialized area. Even within a neurosurgical unit, only a few practitioners will have extensive experience of it. Smith and Hirsch have addressed the anatomy and pathophysiology of the pituitary gland, as well as the preoperative preparation and intraoperative management of these patients.[8] Acromegalic patients are rare, but they may present on any operating list (possibly undiagnosed), and an anaesthetist must be able to manage them appropriately.

Every trained anaesthetist should also be able to manage patients competently with any form of diabetes mellitus. Much is now known about the actions of insulin in health and disease. The historical background

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to this knowledge is interesting; it is described in a logical manner by Sonksen and Sonksen.[9] 'What goes wrong in diabetes' is explained; the metabolic sequelae must be understood for appropriate management of these complex patients in the accident and emergency department, the operating theatre or the intensive care unit. Perioperative management of diabetic patients is often suboptimal: this is inexcusable. McAnulty, Robertshaw and Hall[10] provide a systematic and clear approach to the anaesthetic management of these patients which, if followed, should avoid many of the postoperative problems which diabetics unnecessarily develop (when their care is only being supervised by inexperienced, non-anaesthetic trainee doctors and a paucity of nurses).

Perhaps the most esoteric of endocrine tumours are those found in the gastrointestinal tract. Many anaesthetists will never encounter patients with such tumours of the pancreas as gastrinomas, glucagonomas or somatostatinomas in a lifetime of clinical practice. But they may be presented with patients with multiple endocrine neoplasia including, for instance, carcinoma of the thyroid gland, which can also involve the gut. Diagnosis can often be elusive in these patients and expert anaesthetic knowledge in this area is rare. Holdcroft provides it in a wide-ranging review of hormones and the gut.[11]

Drugs used in anaesthesia may, albeit rarely, produce an atypical response which is potentially fatal. The classic example is malignant hyperthermia.[2] The neuroleptic malignant syndrome (NMS) is an altered response to neuroleptic drugs. It most commonly presents in psychiatric patients, to intensivists rather than anaesthetists. But a relationship has been suggested between NMS and malignant hyperthermia and this topic is discussed by Adnet and colleagues.[12] The adverse metabolic effects of recreational drugs are poorly detected and treated. They are primarily managed in accident and emergency departments, but may present to intensivists and anaesthetists. Their complexities are well described by Henry.[13]

We hope that you will find this postgraduate issue interesting and useful. We think it will help all of us to practice anaesthesia more effectively and appropriately in the next millennium, even in patients with exceptionally challenging or unusual endocrine disease.

P. M. Hopkins
Academic Unit of Anaesthesia
St James University Hospital
Leeds LS9 7TF

J. M. Hunter
Department of Anaesthesia
University of Liverpool
Duncan Building, Daulby Street
Liverpool L69 3GA

References

1. James MFM, Hift RJ. Porphyrias. *Br J Anaesth* 2000; **85**: 143–53
2. Hopkins PM. Malignant hyperthermia: advances in clinical management and diagnosis. *Br J Anaesth* 2000; **85**: 118–28
3. Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000; **85**: 109–17
4. Adams JP, Murphy PG. Obesity in anaesthesia and intensive care. *Br J Anaesth* 2000; **85**: 91–108
5. Farling PA. Thyroid disease. *Br J Anaesth* 2000; **85**: 15–28
6. Mihai R, Farndon JR. Parathyroid disease and calcium metabolism. *Br J Anaesth* 2000; **85**: 29–43
7. Prys-Roberts C. Phaeochromocytoma—recent progress in its management. *Br J Anaesth* 2000; **85**: 44–57
8. Smith M, Hirsch NP. Pituitary disease and anaesthesia. *Br J Anaesth* 2000; **85**: 3–14
9. Sonksen P, Sonksen J. Insulin—understanding its action in health and disease. *Br J Anaesth* 2000; **85**: 69–79
10. McAnulty GR, Robertshaw HJ, Hall GM. Anaesthetic management of patients with diabetes mellitus. *Br J Anaesth* 2000; **85**: 80–90
11. Holdcroft A. Hormones and the gut. *Br J Anaesth* 2000; **85**: 58–68
12. Adnet P, Lestavel P, Krivosic- Horber R. Neuroleptic malignant syndrome. *Br J Anaesth* 2000; **85**: 129–35
13. Henry J. Metabolic consequences of drug misuse. *Br J Anaesth* 2000; **85**: 136–42

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Pituitary disease and anaesthesia

M. Smith and N. P. Hirsch

Department of Neuroanaesthesia, The National Hospital for Neurology and Neurosurgery, University College London Hospitals, Queen Square, London WC1N 3BG, UK

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The perioperative anaesthetic care of patients presenting for pituitary surgery requires careful preoperative assessment and meticulous per- and postoperative management using principles common to all intracranial procedures. Particular problems in such patients relate to primary hormonal hypersecretion and its complications, and to mass effects of the tumour. Knowledge of the normal anatomy and physiology of the pituitary gland is essential to allow an understanding of the pathophysiological effects relevant to anaesthesia and of the potential complications that might arise during and after surgery. The aim of this review is to present the issues which are crucial for the safe anaesthetic management of these challenging patients.

Anatomy and physiology

Anatomy

The pituitary gland consists of two histologically distinct parts: the large, vascular, pink anterior lobe or adenohypophysis and the smaller, grey-white posterior lobe or neurohypophysis. Embryologically, the anterior lobe of the pituitary develops from the ventral ridges of the developing neural tube which are pushed into their resting position by Rathke's pouch. A downgrowth from the floor of the third ventricle of the brain forms the posterior pituitary. The gland averages 6 mm high, 13 mm wide and 9 mm anteroposteriorly; it increases in size during growth spurts and pregnancy. It lies within the pituitary fossa or sella turcica, a depression in the skull base lined with dura mater. The floor and anterior wall of the sella are formed by the roof of the sphenoid air sinus, the posterior wall by the clivus and the lateral walls by the cavernous sinuses which contain the carotid arteries and the third, fourth and sixth cranial nerves (Fig. 1). The roof of the fossa is bounded by the diaphragma sella, an invagination of dura through which the pituitary stalk passes.

Physiology

The traditional method of classifying pituitary cell types by their staining properties (i.e. chromophobes, acidophils and basophils) has largely been abandoned. More recent immunocytochemical techniques allow identification of at least five distinct cell types within the anterior lobe. Somatotrophs account for about 50% of the cells and produce growth hormone. Prolactin-producing lactotrophs account for a further 10–25% and adrenocorticotrophic hormone (ACTH)-producing corticotrophs for another 15%. Melanocyte-stimulating hormone (MSH) is an analogue of ACTH. The other cell types are thyrotrophs (5–10%), which produce thyrotrophin (TSH), and gonadotrophs (10%), which produce follicle-stimulating and luteinizing hormones (FSH and LH). There are also functionally inert cells (null cells) within the gland and these may give rise to non-functioning pituitary adenomas.

Production and release of anterior pituitary hormones are under the control of the hypothalamus. Axons from hypothalamic neurones terminate on the median eminence where a system of fenestrated capillaries carries arterial blood down to the anterior pituitary through the hypophyseal portal system. Peptide hormones stimulate or inhibit release of the corresponding pituitary hormones. Prolactin release is stimulated by prolactin-releasing hormone (PRH) and inhibited by 'prolactin-inhibiting hormone', now known to be dopamine. These are secreted by medial regions of the hypothalamus. Growth hormone release is promoted by growth hormone releasing hormone (GRH) and inhibited by somatostatin; these are both produced in the ventromedial hypothalamus. Thyroid-releasing hormone (TRH), from ventral hypothalamic areas, stimulates the production and release of TSH. Similarly, corticotrophic hormone (CRH) stimulates ACTH release.

The anterior pituitary hormones affect specific target organs and tissues. In women, prolactin causes milk secretion from the breast after oestrogen and progesterone priming. In men, its role is unclear. Growth hormone acts on a wide variety of tissues, both directly and through release of insulin-like growth factor I (IGF-I). This is released

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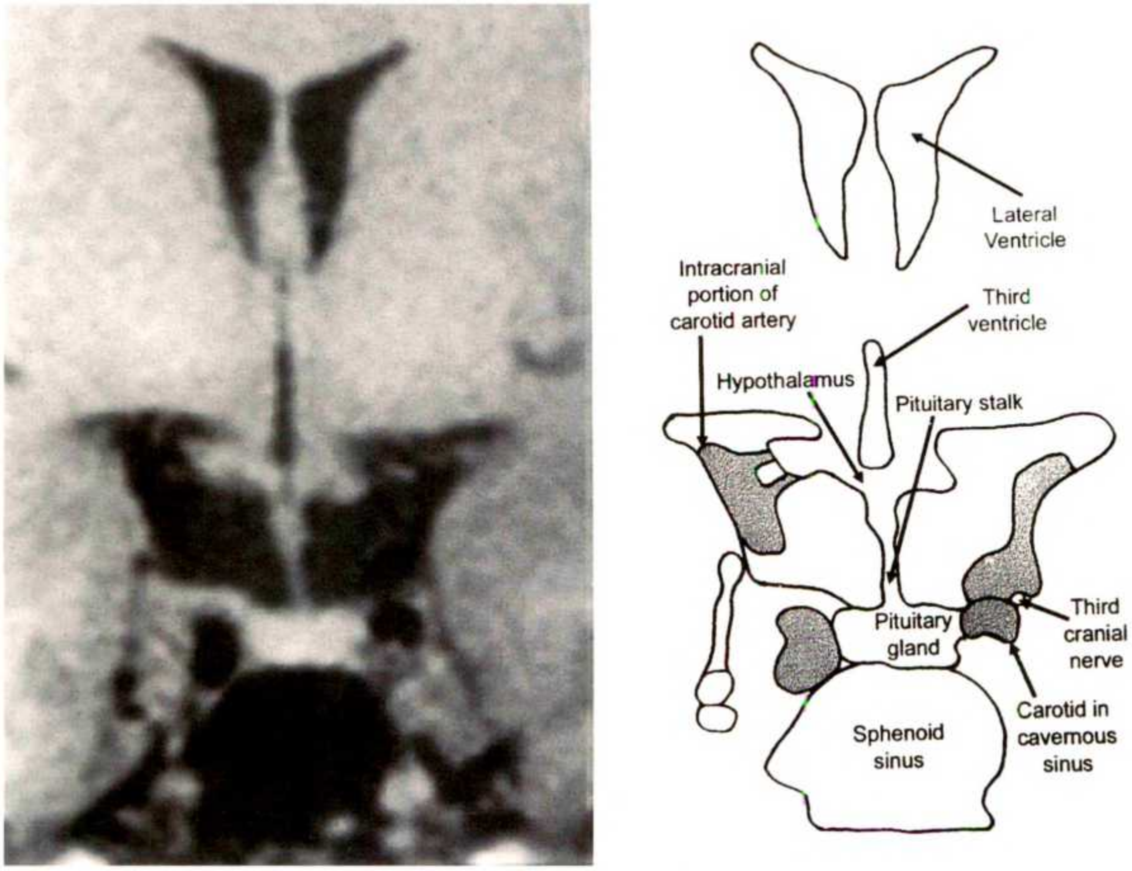

Fig 1 Coronal, T1-weighted, enhanced MRI showing pituitary gland and its anatomical relations.

principally from the liver in response to the presence of growth hormone. In addition to stimulating bone and cartilage growth, growth hormone and IGF-I increase protein synthesis and lipolysis whilst decreasing insulin sensitivity and causing Na^+ retention. TSH stimulates iodine binding by the thyroid gland and increases synthesis and release of triiodothyronine (T_3) and thyroxine (T_4). Blood flow to the thyroid gland increases under the influence of TSH, and chronically elevated concentrations result in enlargement of the gland. ACTH acts on high-affinity membrane receptors of adrenocortical cells. Stimulation results in increased concentrations of intracellular cholesterol, which is converted to cortisol within the mitochondria before release into the circulation. FSH causes early maturation of ovarian follicles and both FSH and LH allow final maturation. Surges in LH are responsible for ovulation. In men, FSH stimulates spematogenesis and LH causes testosterone secretion.

Anterior pituitary hormones are under feedback control. Growth hormone increases circulating IGF-I which in turn directly inhibits growth hormone secretion from the pituitary. It also stimulates somatostatin secretion. Thyroid hormones feedback to inhibit TRH and TSH, and cortisol inhibits CRH and ACTH. Secretion of the gonadotrophic hormones FSH and LH is controlled by a single releasing factor, luteinizing hormone releasing factor (LHRH). The feedback from gonadal hormones at the pituitary and hypothalamus may be inhibitory or stimulatory. The significance of MSH in humans is unclear, but it is controlled by the hypothalamus through stimulatory and inhibitory factors.

In addition to the 'classic' hormones described above, the pituitary secretes a number of other peptides, including vasoactive intestinal peptide, chorionic gonadotrophin, substance P and renin. Such diversity reflects the functional complexity of the gland.[40]

The posterior lobe of the pituitary is made up of pituicytes which, in keeping with its embryological origins, are similar to glial cells. The posterior pituitary is responsible for the storage and release of oxytocin and vasopressin, which are hormones synthesized in the paraventricular and supraoptic nuclei of the hypothalamus.

Pituitary pathology

Most pituitary tumours arise from the anterior part of the gland. The majority are benign adenomas and histologically resemble normal pituitary gland.[37] Proposed mechanisms of tumour development include malfunction of normal growth-regulating genes, abnormalities of tumour suppressor genes and alterations in genes controlling programmed cell death.[38] Pituitary adenomas account for 10–15% of intracranial neoplasms; three-quarters of them secrete inappropriate amounts of pituitary hormones. Tumours arising primarily from the posterior pituitary are extremely rare and this review will concentrate on anterior pituitary tumours.

The prevalence of pituitary tumours is approximately 200 per million of the population[20] but unselected post-mortem studies suggest an incidence of 10–27%.[8] The majority are therefore asymptomatic.

Presentation

Pituitary lesions may present in a variety of ways:[39 41] (i) hormonal hypersecretion syndromes, such as hyperprolactinaemia, acromegaly and Cushing's disease; (ii) mass effect, for example visual disturbance or raised intracranial pressure; (iii) non-specific, for example infertility, headache, epilepsy or pituitary hypofunction; (iv) incidental, such as those detected during imaging for other conditions.

Rarely, a patient may present with pituitary apoplexy following haemorrhage into an adenoma. Sudden and dramatic endocrine alterations are associated with headache, signs of meningism, visual impairment and ophthalmoplegia and other evidence of an intracranial mass lesion.

Hormonal hypersecretion syndromes

Hormonal hyperactivity usually occurs secondary to overproduction of hormones by a discrete adenoma. Prolactinomas occur most commonly. Adenomas producing acromegaly and Cushing's disease are rarer. A non-functioning (i.e. non-hormone-secreting) adenoma can increase prolactin concentrations by compressing the pituitary stalk. This 'stalk effect' in turn reduces transfer of prolactin-inhibiting factor (dopamine) from the hypothalamus to the pituitary.

Mass effect

Mass effect of a tumour on adjacent structures is more likely to occur with non-functioning macroadenomas (>1 cm in diameter). The structures most commonly affected lie adjacent to the pituitary and include optic nerves and chiasm (Fig. 2). Compression of the chiasm results characteristically in bitemporal hemianopia, although in the early stages upper quadrant defects only may be discernible. Occasionally, a third cranial nerve palsy may occur, especially in cases of pituitary apoplexy. Large tumours may also impede cerebrospinal fluid circulation, resulting in hydrocephalus and raised intracranial pressure.

Non-specific

Non-specific presentations include infertility, epilepsy or pituitary hypofunction. Hormonal underactivity results from compression of normal pituitary tissue by a non-functioning adenoma, by haemorrhage into the pituitary resulting in pituitary apoplexy or, more rarely, by postpartum pituitary infarction (Sheehan's syndrome). Most commonly, however, hypopituitarism is the result of pituitary surgery or radiotherapy.

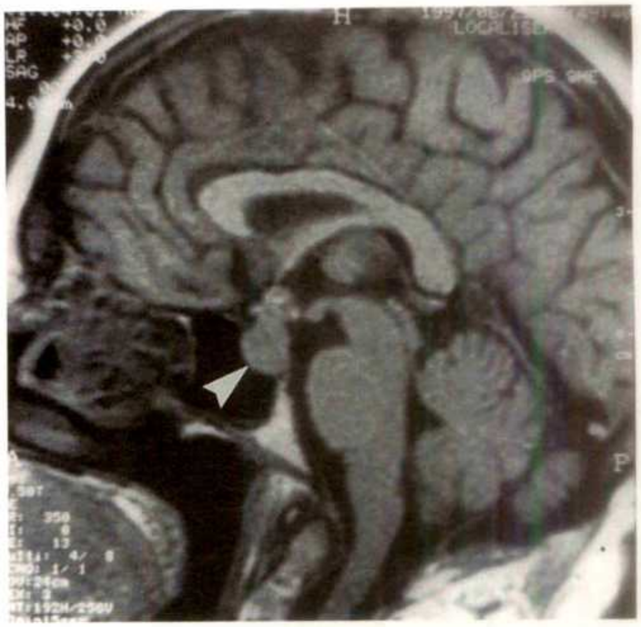

Fig 2 Sagittal, T1-weighted MRI showing large pituitary macroadenoma (arrow) with suprasellar extension.

Incidentalomas

Pituitary tumours, often called 'incidentalomas', may present as an incidental finding during investigation of an unrelated condition;[50 71] this is the result of the increased sensitivity of CT and MRI techniques. Incidental demonstration of a pituitary mass occurs in >10% of patients undergoing cranial imaging,[39] an unsurprising finding as occult pituitary adenomas have been reported in up to 27% of post-mortem examinations of patients dying from unrelated causes.[8]

Preoperative diagnosis and management of pituitary tumours

All patients need measurement of basal prolactin concentrations, thyroid function tests and a high quality MRI. Elevated prolactin concentrations in the absence of treatment with dopamine antagonists, hypothyroidism or other causes of secondary hyperprolactinaemia are an indication for pituitary imaging. Thyroid function is of fundamental importance. Pituitary adenomas rarely cause thyroid hypofunction, but it is important to exclude the diagnosis. Primary hypothyroidism can cause pituitary enlargement and hyperprolactinaemia, while both primary and secondary hypothyroidism may make anaesthesia hazardous. Abnormalities of thyroid function should therefore be treated before surgical intervention. MRI has superseded CT as the imaging technique of choice because of its ability to differentiate between soft tissues in the assessment of the spread of macroadenomas and its superior ability to visualize microadenomas. CT remains valuable in the assessment of bony invasion. The management of specific tumour types is discussed below and has been reviewed in detail elsewhere.[31 39]

Prolactin-secreting tumours

Prolactin-secreting tumours account for more than half of functioning pituitary tumours. The majority are microadenomas (<1 cm) and 90% occur in women. Females present typically with secondary amenorrhoea and galactorrhoea, although the latter may be absent if oestrogen concentrations are low. Men with prolactin-secreting tumours can present with impotence and a decreased sperm count and such tumours may be diagnosed during investigation of infertility.

Prolactin-producing macroadenomas (>1 cm) are more common in men and may present with visual field defects secondary to pressure effects of the tumour, rather than with fertility problems.

Diagnosis

MRI of the pituitary fossa identifies the presence of a tumour and an elevated plasma prolactin concentration confirms the diagnosis.[52] The upper limit of normal for basal circulating prolactin varies depending upon the assay but concentrations of >400 mU litre^{-1} (20 ng ml^{-1}) are generally accepted to be elevated. Plasma concentrations correlate well with tumour size. Prolactin-secreting microadenomas generate prolactin concentrations of 1000–4000 mU litre^{-1}, whereas concentrations of >6000 mU litre^{-1} are usually associated with macroadenomas. Large, non-functioning tumours can also increase prolactin concentrations by compressing the pituitary stalk (see above) but under such circumstances the prolactin concentration rarely exceeds 3000 mU litre^{-1}. As prolactin is a stress hormone, its plasma concentration may rise during venesection. If possible, an intravenous cannula should be placed and blood removed some hours later.

Treatment

The first-line treatment of prolactinomas is with a dopamine agonist, such as bromocriptine, titrated against plasma prolactin concentration.[32 43 52] Bromocriptine should be introduced at a low dose (1 mg) with food and increased to 5–15 mg daily until optimum control is achieved. Cabergoline is an alternative to bromocriptine.[32] Medical therapy is curative in <95% of patients, in whom prolactin concentrations are restored to normal.[4] Surgical removal of the adenoma is indicated in the minority of patients who do not respond to dopamine agonists[52] or in the rare cases when side-effects (nausea, lethargy or nasal stuffiness) limit their use.[49] In patients with a macroadenoma, morning cortisol concentration should be checked if symptoms suggest hypopituitarism, although this is rare. If this concentration is borderline, a Synacthen test should be performed. Monitoring of visual field and acuity is vital. First-line therapy with bromocriptine should be reviewed after 1 week to check that field defects have not deteriorated. Many patients with large tumours do respond to medical treatment, and in 75% of such patients, visual defects are abolished.[4] Although there is no evidence of teratogenicity, dopamine agonists are usually stopped during pregnancy. Symptomatic enlargement of treated microadenomas is extremely rare but monitoring of visual fields and sequential MRI will detect the 15% of macroadenomas that grow significantly during this time.[51] In these patients drug therapy may be reintroduced as this does not affect the outcome of pregnancy.[48]

Growth hormone-secreting tumours

Excess secretion of growth hormone produces acromegaly in the adult and gigantism before epiphyseal closure. The annual incidence of acromegaly is six to eight cases per million of the population. The clinical syndrome is usually insidious in onset and is characterized by enlargement of the jaw, hands and feet and increased soft tissue growth secondary to elevation of growth hormone concentration (Fig. 3). Associated complications of the disease, such as diabetes mellitus and hypertension, are often the first medical indications of acromegaly. The common clinical signs and symptoms are shown in Table 1.

Diagnosis

A random serum growth hormone concentration of >10 mU litre^{-1} (5 ng ml^{-1}), failure of suppression of growth hormone concentrations to <2 mU litre^{-1} (1 ng ml^{-1}) following a 75 g oral glucose load and elevated IGF-I are diagnostic of acromegaly. An isolated measurement of growth hormone concentration may be misleading because it is released in bursts and has a short half-life. IGF-I, a somatomedin through which growth hormone exerts many of its effects, has a longer half-life and is therefore a useful measure of mean growth hormone activity.

Treatment

The primary treatment is surgery, with or without subsequent radiotherapy. A few patients respond to dopamine agonists and, in such cases, growth hormone and IGF-I concentrations can be normalized without surgery.[3] Long-acting analogues of somatostatin (such as octreotide) may have a place in those who fail to respond to dopamine agonists but the need for parenteral administration and the high incidence of gallstones limits their use.[35] Recently, a new slow-release preparation, somatuline, given by injection every 1–2 weeks has been investigated.[30]

ACTH-secreting tumours

The annual incidence of ACTH-producing pituitary tumours is two to four per million of the population. These tumours account for 4% of functioning pituitary adenomas and 80%

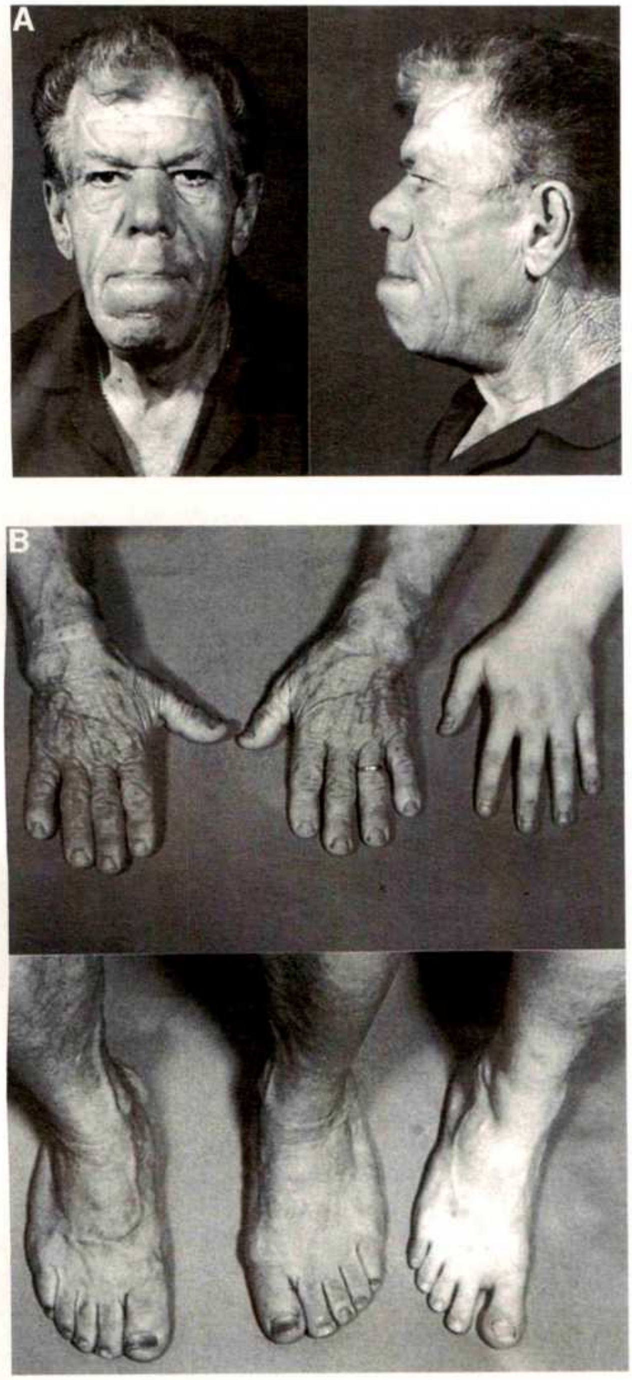

Fig 3 Clinical features of acromegaly.

occur in women. The majority are microadenomas. High concentrations of cortisol cause Cushing's syndrome, which may occur secondary to treatment with glucocorticoid drugs (the most common cause), an adrenal tumour, ectopic production of ACTH associated with a neoplasm, or a pituitary tumour. The clinical condition resulting from excess ACTH production by a pituitary adenoma is called Cushing's disease. Whatever the cause of the excess circulating cortisol, Cushing's syndrome is characterized by widespread effects (Table 2).

Table 1 Clinical features of acromegaly

Affected area	Clinical features
Face	Increase in size of skull and supraorbital ridges; enlarged lower jaw; increase in spacing between teeth/malocclusion
Hands and feet	Spade-shaped; carpal tunnel syndrome
Mouth/tongue	Macroglossia; thickened pharyngeal and laryngeal soft tissues; obstructive sleep apnoea
Soft tissue	Thick skin; doughlike feel to palm
Skeleton	Vertebral enlargement; osteoporosis; kyphosis
Cardiovascular	Hypertension; cardiomegaly; impaired left ventricular function
Endocrine	Impaired glucose tolerance; diabetes
Other	Arthropathy; proximal myopathy

Table 2 Clinical features of Cushing's syndrome

Appearance	Redistribution of body fat; 'moon' face; truncal or 'buffalo' obesity
Musculoskeletal	Proximal myopathy; osteoporosis; vertebral collapse
Skin	Purple striae on abdomen, buttocks, thighs; easy bruising and fragile skin; hirsutism; acne
Endocrine	Impaired glucose tolerance; diabetes
Cardiovascular	Hypertension; ECG abnormalities; left ventricular hypertrophy
Metabolic	Hypernatraemia; hypokalaemia; alkalosis
Other	Sleep apnoea; gastointestinal reflux; renal stones; masculinization; mental disturbance

Diagnosis

Diagnosis may be complex and should be carried out in a specialist centre. Urinary concentrations of free cortisol, loss of diurnal cortisol control and lack of response to overnight dexamethasone suppression are primary screening procedures.[17] High concentrations of circulating ACTH are indicated by urinary cortisol >275 nmol 24 h^{-1} and failure to suppress serum cortisol concentration to <138 nmol $litre^{-1}$ following an oral dose of dexamethasone 1 mg the night before sampling. ACTH concentrations should be measured under such circumstances. If ACTH is undetectable, this suggests an adrenal tumour; concentrations between 10 and 100 ng $litre^{-1}$ suggest pituitary-dependent disease while concentrations >200 ng $litre^{-1}$ suggest ectopic ACTH secretion. Often, cortisol concentrations do not fall into the normal range and further stimulatory or suppression tests may be required. An exaggerated secretory response to the administration of CRH occurs in pituitary disease and a reduced or absent response in adrenal and ectopic ACTH disease. The high-dose dexamethasone suppression test involves giving dexamethasone 2 mg every 6 h for 48 h. Pituitary-dependent Cushing's syndrome usually responds with a fall of both early morning plasma cortisol and urinary free cortisol concentrations on the second day. Selective inferior petrosal sinus sampling and measurement of ACTH concentrations following CRH stimulation is the final confirmatory test for pituitary Cushing's syndrome.[59]

Treatment

Primary treatment is surgical, and is curative in <80% of patients. Pretreatment with metyrapone or betaconazole reverses the side-effects of increased concentrations of circulating cortisol, which used to cause significant perioperative morbidity and mortality.[15] If surgery is not possible or has failed, radiotherapy is a secondary option. This may be accompanied by bilateral adrenalectomy and mineralocorticoid and glucocorticoid replacement therapy. However, adrenalectomy carries the risk of Nelson's syndrome (hyperpigmentation as a result of MSH secretion and compression of parapituitary structures) in 20% of patients. Pituitary radiotherapy and adrenalectomy are highly effective in children.

Glycopeptide (TSH, FSH and LH)-secreting tumours

TSH-secreting pituitary adenomas are extremely rare, aggressive tumours whose first-line treatment is surgical. The diagnosis is confirmed by the presence of hyperthyroidism in association with elevated plasma concentrations of TSH. The diagnosis may be missed by the unwary if it is not appreciated that TSH concentrations within the normal range are inappropriately high in the presence of consistently elevated concentrations of circulating thyroid hormones.

Gonadotroph adenomas present usually as inactive adenomas but may present rarely with premature puberty or the resumption of menstrual bleeding in post-menopausal women. Elevated prolactin concentrations may occur in <80% of endocrinologically inactive adenomas because of compression of the pituitary stalk. Macroadenomas may present with compression of sella structures and secondary hypopituitarism. Again, first-line therapy is surgical.

Non-functioning tumours

Approximately 25% of pituitary tumours are non-functioning. They usually present with visual disturbance secondary to chiasmal compression or headache caused by increased intracranial pressure. Ophthalmological assessment is mandatory for all tumours extending into the suprasellar area. If there are no symptoms or signs of pressure effects, it is acceptable simply to review patients on a regular basis using measurements of visual fields and MRI. Increase in tumour size, deterioration in visual fields or onset of other symptoms requires surgical decompression, usually in combination with postoperative radiotherapy. Rarely, non-functioning tumours may present with panhypopituitarism or pituitary apoplexy. The latter is associated with abrupt onset of severe headache and may mimic subarachnoid haemorrhage. Hormone concentrations are usually normal, with the exception of raised prolactin concentrations resulting from the 'stalk effect'. Cortisol status should be checked if there are signs of hypopituitarism.

Preoperative assessment

In addition to the usual general pre-anaesthetic assessment of a neurosurgical patient, preoperative review of patients scheduled for pituitary surgery should include an assessment of: visual function; signs and symptoms of raised intracranial pressure; the patient's endocrine studies; and the effects of hormonal hypersecretion. Those with acromegaly or Cushing's syndrome are particularly likely to have co-morbidities and preoperative assessment should be directed accordingly.

Acromegaly

Growth hormone hypersecretion affects not only the extremities but also the soft tissues of the mouth, tongue and laryngeal cartilages. The anatomical changes that may result include prognathism and macroglossia. Thickening of the pharyngeal and laryngeal soft tissues and vocal cords, reduction in the size of the laryngeal aperture, hypertrophy of the periepiglottic folds and recurrent laryngeal nerve palsy also occur.[19] About one-quarter of acromegalic patients have an enlarged thyroid, which may compress the trachea.[53] Acromegaly is recognized as one of the causes of difficulty in airway management and tracheal intubation.[7 9 28 34 55 60 72] Careful airway assessment using conventional criteria is essential and preoperative evaluation with indirect laryngoscopy has been recommended.[34 54] Sleep apnoea is a rare complicating factor of acromegaly but is associated with a high risk of perioperative airway compromise.[9 62] Upper airway obstruction is the major cause of sleep apnoea in acromegaly[25] but central depression may also contribute.[61] It is not surprising, therefore, that the risk of death from respiratory failure is threefold greater in acromegaly.[54 81] A history of loud snoring and daytime hypersomnolence should alert the anaesthetist to the possibility of sleep apnoea. The response to resection of the underlying pituitary tumour is unclear,[62] but vocal cord function reverts towards normal within 10 days of successful surgery.[79]

Hypertension occurs in 30% of patients with acromegaly but usually responds to therapy. Myocardial hypertrophy and interstitial fibrosis are common in acromegalic patients and may be associated with reduced left ventricular function.[67] The impairment in left ventricular function may persist in those successfully treated by surgery if the disease has been longstanding. Left ventricular size often returns to near-normal after surgery and the failure of an associated return of normal function may reflect persistence of interstitial fibrosis.[67] Glucose intolerance is encountered frequently and overt diabetes occurs in 25% of acromegalic patients.

Cushing's syndrome

Increased renin–angiotensin activity and elevated blood volume result in hypertension in 85% of these patients. This can be difficult to bring under control. ECG abnormalities (high voltage QRS complexes and inverted T waves) are common but revert to normal after curative pituitary surgery.[74] Left ventricular hypertrophy and asymmetric septal hypertrophy are observed frequently in patients with Cushing's syndrome. The aetiology of this hypertrophy is unknown but, because it occurs more commonly than in essential and other secondary hypertension syndromes, it is likely that excessive plasma cortisol is a contributing factor.[74] Curative surgery results in improvement in left ventricular function in the majority of cases. Sleep apnoea is also a common finding in Cushing's syndrome. In a recent investigation of Cushing's patients using polysomnography, mild sleep apnoea was observed in 32% and severe sleep apnoea in 18%.[68] Glucose intolerance or frank diabetes occurs in 60% of patients and is related to reduced insulin secretion and non-insulin-mediated glucose disposal in the presence of elevated insulin concentrations. Renal calculi are a common association. Obesity and gastroesophageal reflux are frequently encountered and prescription of H_2 antagonists may be appropriate. High concentrations of glucocorticoids are immunosupressive and the presence of coexisting infection should be considered. Finally, the fragile skin and easy bruising typically found in these patients can make intravenous access problematic.

Surgical approach

The main aim of surgery is tumour removal, which can be achieved in most cases. In practice, near-total tumour removal leads to endocrine remission and debulking achieves chiasmal decompression. Tumour biopsy alone is indicated occasionally. The pituitary fossa can be approached using the transsphenoidal, transethmoidal or transcranial route. The transsphenoidal route is preferred for all but the largest of tumours.[80] It has the advantage of rapid, midline access to the sella with minimal risk of brain trauma or haemorrhage as well as a low incidence of postoperative complications. It can be used even for tumours that extend superiorly outside the sella as long as they are in the midline. Various techniques can be applied (see below) to increase the intracranial pressure transiently and cause the tumour to descend into the sella region from where it can be safely resected. Transsphenoidal access to the pituitary fossa is obtained using a sublabial or endonasal approach. Correct alignment during the approach to the fossa is confirmed by fluoroscopy. Some large tumours, particularly those with lateral growth outside the sella or those that are multilobular, are best resected by subfrontal or pterional craniotomy. A small or non-pneumatized sphenoid sinus is also an indication for craniotomy. The transcranial route carries a high risk of total ablation of the pituitary gland and the need for permanent hormone replacement. Postoperative seizures are also more likely if the subfrontal approach is chosen.

Anaesthetic management

Anaesthesia for surgery to the pituitary region has been reviewed previously.[14 29 45 64] It is not the intention of this review to deal with all aspects of neuroanaesthesia; rather, we consider only the issues relating to pituitary surgery. The general aims of anaesthesia include haemodynamic stability, maintenance of cerebral oxygenation, provision of conditions to facilitate surgical exposure, prevention of intraoperative complications and rapid emergence to facilitate early neurological assessment.

Hormone replacement

Preoperative hormone replacement therapy should be continued into the operative period. In general, hydrocortisone 100 mg should be administered at induction of anaesthesia in all patients undergoing pituitary surgery; however, individual units with wide experience will have developed local protocols for perioperative hormone replacement, particularly for complex conditions such as Cushing's disease.

Airway management

Careful preoperative assessment alerts the anaesthetist to the possibility of difficulties with airway management and tracheal intubation. Ventilation with a bag and mask is generally straightforward in acromegalic patients although an oral airway may be required.[27] Four grades of airway involvement have been described in acromegaly: grade 1, no significant involvement; grade 2, nasal and pharyngeal mucosa hypertrophy but normal cords and glottis; grade 3, glottic involvement including glottic stenosis or vocal cord paresis; and grade 4, combination of grades 2 and 3, i.e. glottic and soft tissue abnormalities.[72] Tracheostomy has been recommended for grades 3 and 4 but others have suggested that fibreoptic laryngoscopy is a safe alternative.[60] However, difficulty with fibreoptic intubation in acromegalic patients has recently been described.[27] In one patient in this study, the larynx could not be viewed with either a Macintosh laryngoscope or a fibreoptic laryngoscope but the trachea was intubated blindly with the help of an introducer. In the authors' experience of >150 pituitary operations per annum at the National Hospital, airway management and tracheal intubation proceed uneventfully in the majority of patients if large face masks and long-bladed laryngoscopes are used. However, fibreoptic intubation should be considered in patients in whom difficult airway management is predicted.[46] The intubating laryngeal mask airway has also been used successfully in a patient with acromegaly.[69] Equipment for tracheostomy should be available if airway changes are advanced.[72]

Following intubation, the mouth and posterior pharynx should be packed before surgery begins. This will not only prevent bleeding into the glottic region during surgery, but also entry of blood and secretions into the stomach which may precipitate postoperative vomiting. The tracheal tube must be positioned to allow the neurosurgeon access to the chosen incision site.

Preparation of the nasal mucosa

Most surgeons prefer to introduce a vascoconstricting agent into each nostril before transsphenoidal surgery. Traditionally, mixtures of cocaine and epinephrine have been used.[47] Although the addition of epinephrine limits systemic absorption,[5] the use of cocaine-containing preparations continues to be associated with a risk of arrhythmias and myocardial infarction.[16 57] Xylometazoline, a sympathomimetic amine acting at alpha adrenoreceptors, may be a safer alternative. It produces rapid and prolonged vasoconstriction lasting up to 8 h and, when combined with lidocaine, its effects are equivalent to those of cocaine.[10]

Lumbar drain

Some surgeons request insertion of a lumbar drain in patients with significant suprasellar tumour extension. This has two uses. Introduction of 10 ml aliquots of 0.9% saline will, during transsphenoidal surgery, produce prolapse of the suprasellar portion of the tumour into the operative field (see above). In addition, should the dura be breached during the procedure, the catheter can be left in place postoperatively to act as a CSF drain in an attempt to control any leak of CSF.[63]

Position

Transsphenoidal surgery is carried out with the patient supine with a moderate degree of head-up tilt. The head may be turned slightly to the side to facilitate surgical access. The surgeon may stand at the top of the table behind the head, or to the right or left. The tracheal tube and anaesthetic circuit should be placed away from the surgical field. As frequent radiography is required, the C-arm of the image intensifier is usually left in position throughout surgery. All theatre personnel should wear appropriate protection. Transcranial surgery to the pituitary area is also performed with the patient in the supine position. Subfrontal surgery is carried out with the head in the midline position but pterional approaches require the head to be turned. Care should be taken to ensure that the neck veins are not obstructed.

Maintenance of anaesthesia

Any anaesthetic technique suitable for intracranial procedures is acceptable, but the presence of increased intracranial pressure requires special attention. Choice of anaesthetic technique is usually determined by personal preference since attention to detail and a meticulous anaesthetic technique are generally more important than the use of specific drugs.[36] The merits of inhalational and total intravenous techniques during neuroanaesthesia have been considered elsewhere.[65 76 78] However, neither is superior to the other under most circumstances.[75] In the presence of raised intracranial pressure, total intravenous anaesthesia and the avoidance of nitrous oxide has been recommended.[44 76] Whichever technique is chosen, it is important that short-acting agents are used to allow rapid recovery at the end of surgery. Drugs such as propofol[65] and sevoflurane[70] clearly fall into this category. During transsphenoidal surgery, ventilation to normocapnia should be employed. Excessive hyperventilation will result in loss of brain bulk and make any suprasellar extension of the tumour less accessible from below. There are periods of intense stimulation during transsphenoidal access to the pituitary fossa. Short-acting opioids should be titrated against blood pressure. The ultra-short-acting opioid, remifentanil, allows maintenance of stable conditions in neurosurgical patients[26 77] and is a useful adjunct during transsphenoidal surgery. Its short context-sensitive half-time ensures rapid offset of action when the infusion is discontinued. Although this will allow rapid emergence from anaesthesia, it is essential that longer-acting opioids are administered before the end of surgery so that patients do not awaken in pain. The administration of intravenous morphine or intramuscular codeine 20–30 min before the end of surgery has been recommended.[36] Bilateral maxillary nerve block with local anaesthesia has also been described as a method of preventing the hypertensive response to transsphenoidal surgery during general anaesthesia.[13]

Monitoring

Monitoring during pituitary surgery will include ECG, Sp_{O_2}, endtidal carbon dioxide and direct arterial blood pressure. Co-morbidities, especially in Cushing's patients, may require additional invasive cardiovascular monitoring. If cavernous sinus invasion is suspected, and the patient is positioned in a steep head-up tilt, monitoring for the possibility of venous air embolus should be considered.[56] Visual evoked potential (VEP) recording has been recommended for tumour surgery in the region of the visual pathways. Although VEP recording is widely used in diagnosis, its use in the operating room has been limited by the high incidence of false-positive and false-negative results.[21] Furthermore, the exquisite sensitivity of VEPs to anaesthetic agents has led some to suggest that, during anaesthesia, the waveforms are too unstable to be of much practical use.[11] In a recent study, peroperative VEP monitoring resulted in greater improvement in field defects after transsphenoidal pituitary surgery although postoperative improvement in visual acuity was not affected.[12]

Prophylactic antibiotics

There remains debate over this issue. Although some neurosurgeons do not use prophylaxis and claim no problems, most units in the UK have adopted a consensus policy.[1] This involves the administration of a cephalosporin (e.g. cefuroxime 1.5 g) at induction of anaesthesia and every 3 h thereafter during surgery. No further doses are given in the postoperative period, to minimize the development of resistant organisms.

Operative complications

Complications during transsphenoidal surgery are rare. Pituitary tumours are not usually vascular and the slight venous ooze that inevitably occurs can be controlled easily by gentle pressure. Other, more serious complications, occur if the neurosurgeon loses the anatomical landmarks of the fossa during transsphenoidal surgery. Deviation laterally may result in carotid damage, which is usually controllable by packing. Because of the risk of development of a false aneurysm in the postoperative period, carotid angiography should be performed. If an aneurysm is confirmed, it should be treated by endovascular radiological techniques or by clipping to prevent later rupture. If the surgeon misses the fossa altogether, damage to the pons may occur. This has serious consequences. The risk of these complications is minimized by frequent radiographic confirmation of the position during transsphenoidal surgery.

Transcranial pituitary surgery carries similar risks to other intracranial procedures. Frontal lobe ischaemic damage because of prolonged traction can be minimized by careful placement and intermittent release of retractors. Trauma to the carotid artery or optic chiasm can also occur. The incidence of postoperative seizures is higher after subfrontal surgery than after other approaches. Some recommend the use of prophylactic anticonvulsant therapy[58] but others find the evidence unconvincing.[22] Anosmia may also occur because of damage to the olfactory tract.

Emergence from anaesthesia

Smooth and rapid emergence from anaesthesia following neurosurgery is essential to allow early neurological assessment and maintenance of stable respiratory and cardiovascular variables.[6] This is facilitated by the use of short-acting agents for maintenance of anaesthesia. At the end of transsphenoidal surgery, extubation is carried out after return of spontaneous ventilation, pharyngeal suction under direct vision, removal of the throat pack and return of laryngeal reflexes. Smooth emergence can be facilitated by placing the patient in a semi-seated position and ensuring that there is a response to verbal commands before extubation. Care should be taken to ensure that nasal packs or stents, put in place at the end of surgery, do not become dislodged during extubation.

Postoperative care

This consists of careful airway management, provision of adequate postoperative analgesia, appropriate fluid and hormone replacement and careful monitoring for postoperative complications. Following transsphenoidal surgery, patients seldom require prolonged nursing on a one-to-one basis unless there are significant co-morbidities. Following a period in the recovery room, the patient may usually be returned to a general ward. After transcranial pituitary surgery, patients should be managed in a neurosurgical intensive care or high-dependency unit for at least 24 h.

Airway management

Maintenance of a clear airway can be difficult and requires careful attention. The presence of blood in the nasopharynx and oropharynx, nasal packs and the predisposition of acromegalic patients to airway obstruction all tend to compromise airway patency. All patients must, therefore, be closely observed after transsphenoidal surgery until fully awake. Airway management is particularly important in acromegalic patients, especially in those with a history of sleep apnoea. Such patients should be nursed in a high-dependency environment through the first postoperative night when hypoventilation and respiratory obstruction may occur. Usual treatment options such as nasal CPAP cannot be applied after transsphenoidal surgery. Acute pulmonary oedema secondary to airway obstruction has been reported in this patient group.[23]

Postoperative analgesia

Transsphenoidal surgery usually causes only moderate postoperative pain but the feeling of nasal congestion from the presence of nasal packs is frequently distressing to patients. Craniotomy is more painful and stronger analgesia is required.[73] Codeine phosphate has been the mainstay of postoperative analgesia in neurosurgical patients for many years because it was considered to be relatively free from unwanted side-effects such as sedation, respiratory depression and pupillary changes. However, it is likely that this merely reflects underdosage and it is clear that pain after craniotomy can be more severe than previously appreciated.[73] Attitudes to the management of postoperative pain in neurosurgical patients are changing. A recent double-blind study confirmed that intramuscular morphine is not associated with more side-effects after craniotomy and has a longer duration of action than codeine.[24] Intravenous morphine administered via a PCA has been used successfully in neurosurgical patients.[73]

Hormone replacement

It is safest to assume that all patients will require cortisol replacement in the short term. Replacement should be tailed down to maintenance levels within a few days. A standard regimen recommends hydrocortisone 50 mg bd on the first postoperative day, 25 mg bd on the second, reducing to 20 mg in the morning and 10 mg in the evening by the third day.[63] Patients usually leave hospital on this dose although it is higher than the normal replacement of 15 mg in the morning and 5 mg in the evening. The evening dose should be given between 17.00 and 18.00 h. Patients with prolactin-secreting microadenomas can be weaned off hydrocortisone safely within the first few days without risk if ≥20% of the pituitary gland has been left behind at surgery.[63] In Cushing's disease, normal corticotrophs are heavily suppressed and replacement will be required for many weeks or months. Preoperative replacement of other hormones should be continued into the postoperative period, until review by an endocrinologist. Postoperative management by a multidisciplinary team using locally developed protocols is crucial to successful endocrine management.

Postoperative hormone complications

These are rare but require careful and timely treatment.

Diabetes insipidus

This usually develops within the first 24 h and occurs when >80% of neurones synthesizing vasopressin are destroyed or become temporarily non-functional.[66] It should be suspected if the patient is producing >1 litre of dilute urine in 12 h, associated with a plasma Na^+ concentration of >143 mmol $litre^{-1}$. Urine output and specific gravity should be measured routinely after pituitary surgery. If problems develop, regular measurement of plasma and urinary osmolality is required.[18] Modest polyuria in the early postoperative period may be related to delayed excretion of the fluid given during surgery or corticosteroid-induced hyperglycaemia. Patients may feel thirsty after transsphenoidal surgery, but this can be related to mouth breathing because of nasal packs rather than to diabetes insipidus. It is, therefore, essential that the diagnosis of diabetes insipidus is confirmed biochemically before treatment is instituted.[18] A combination of increased plasma osmolality (>295 mosmol kg^{-1}), hypotonic urine (<300 mosmol kg^{-1}) and a high urine output (>2 ml kg^{-1} h^{-1}) are the criteria on which the diagnosis should be based. Diabetes insipidus is easily treated with desmopressin acetate (DDAVP).[18] However, if the patient is awake and has a normal thirst mechanism, it is safest to allow free access to fluid rather than attempt overzealous i.v. fluid and DDAVP replacement. Over-enthusiastic use of DDAVP may lead to hyponatraemia with its attendant problems of confusion, seizures and coma. Most borderline cases of diabetes insipidus resolve spontaneously over a few days, as posterior lobe function recovers. Comatose patients, those with no thirst response and the minority in whom urine volumes are excessively large are at particular risk, both from under-hydration as a consequence of the diabetes insipidus or of over-hydration as a consequence of therapy. Careful treatment with DDAVP will usually be required under such circumstances. The recommended iv/im dose of DDAVP is 0.1 µg repeated as required. In the acute phase, a smaller dose of 0.04 µg i.v. provides an adequate response with a shorter duration of action. An oral preparation and a metered dose nasal spray are also available. Plasma Na^+ concentration and osmolality should be closely monitored until normal water balance has been re-established. Long-term DDAVP therapy is required in only a minority of cases.

Hyponatraemia

The commonest cause of hyponatraemia after pituitary surgery is over-enthusiastic use of DDAVP. Rarely, it may occur because of the syndrome of inappropriate ADH secretion (SIADH) caused by non-specific release of ADH from degenerating posterior pituitary neurosecretory terminals.[33] This results in water retention and secondary loss of urinary Na^+. It is usually transitory and rarely lasts for >7–10 days. It is managed by fluid restriction which should be carefully monitored by regular measurement of plasma electrolytes. Rarely, hyponatraemia after intracranial neurosurgery may be associated not only with natiuresis but also with a tendency to diuresis, leading to a significant contraction of circulating and extracellular volumes. This phenomenon is known as cerebral salt wasting syndrome (CSW) and may be difficult to differentiate from SIADH. However, it is crucial that the diagnosis is made correctly because the treatment regimens of the two conditions are diametrically opposed.[42] In SIADH the problem is one of extracellular volume expansion caused by water retention, and the best approach is to limit water intake to 500–1000 ml day^{-1} depending upon the plasma Na^+ concentration. In CSW, fluid restriction will not correct the hyponatraemia and will, in fact, be harmful because it will further reduce intravascular volume. Hypertonic saline is used to correct the hyponatraemia of CSW. Correction of low Na^+ concentrations should always take place over 24–48 h, at a rate to increase plasma Na^+ concentration by <1 mmol h^{-1}. Too rapid correction may result in central pontine myelinolysis.[2]

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References

1 Antimicrobial prophylaxis in neurosurgery and after head injury. Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy. *Lancet* 1994, **344**: 1547–51

2 Arieff AI. Management of hyponatraemia *Br Med J* 1993; **307**: 305–8

3 Besser GM, Wass JA, Thorner MO. Bromocriptine in the medical management of acromegaly. *Adv Biochem Psychopharmacol* 1980, **23**. 191–8

4 Bevan JS, Webster J, Burke CW, Scanlon MF. Dopamine agonists and pituitary tumour shrinkage. *Endocr Rev* 1992; **13**: 220–40

5 Bromley L, Hayward A Cocaine absorption from the nasal mucosa. *Anaesthesia* 1988; **43**: 356–8

6 Bruder N, Ravussin P. Recovery from anesthesia and postoperative extubation of neurosurgical patients: a review. *J Neurosurg Anesthesiol* 1999: **11**. 282–93

7 Burn JM. Airway difficulties associated with anaesthesia in acromegaly. *Br J Anaesth* 1972; **44**: 413–4

8 Burrow GN, Wortzman G, Rewcastle NB, Holgate RC, Kovacs K. Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series *N Engl J Med* 1981; **304**: 156–8

9 Cadieux RJ, Kales A, Santen RJ, Bixler EO, Gordon R. Endoscopic findings in sleep apnea associated with acromegaly. *J Clin Endocrinol Metab* 1982: **55**: 18· 18–22

10 Campbell JP, Campbell CD, Warren DW, Prazma TU, Pillsbury HC. Comparison of the vasoconstrictive and anesthetic effects of intranasally applied cocaine vs xylometazoline/lidocaine solution *Otolaryngol Head Neck Surg* 1992; **107**. 697–700

11 Cedzich C, Schramm J, Mengedoht CF, Fahlbusch R Factors that limit the use of flash visual evoked potentials for surgical monitoring. *Electroencephalogr Clin Neurophysiol* 1988; **71**: 142–5

12 Chacko AG, Babu KS, Chandy MJ Value of visual evoked potential monitoring during trans-sphenoidal pituitary surgery. *Br J Neurosurg* 1996; **10**: 275–8

13 Chadha R, Padmanabhan V, Rout A, Waikar HD, Mohandas K. Prevention of hypertension during trans-sphenoidal surgery—the effect of bilateral maxillary nerve block with local anaesthetics. *Acta Anaesthesiol Scand* 1997; **41**: 35–40

14 Chan VWS, Tindal S. *Anaesthesia* for transsphenoidal surgery in a patient with extreme gigantism. *Br J Anaesth* 1988; **60**: 464–8

15 Child DF, Burke CW, Burley DM, Rees LH, Fraser TR. Drug control of Cushing's syndrome: combined aminoglutethamide and metyrapone therapy. *Acta Endocrinol* 1976; **82**: 330–41

16 Chiu YC, Brecht K, Dasgupta DS, Mhoon E Myocardial infarction with topical cocaine anaesthesia for nasal surgery. *Arch Otolaryngol Head Neck Surg* 1986; **112**· 988–90

17 Crapo L Cushing's syndrome. a review of the diagnostic tests *Metabolism* 1979, **28**· 955–77

18 Cusick JF, Hagen TC, Findling JW Inappropriate secretion of antidiuretic hormone after transsphenoidal surgery for pituitary tumours. *N Engl J Med* 1984, **311**· 36–8

19 Edge WG, Whitwam JG. Chondro-calcinosis and difficult intubation in acromegaly. *Anaesthesia* 1981; **36**: 677–80

20 Faglia G, Ambrosi B. Hypothalamic and pituitary tumours: general principles In: Grossman A ed *Clinical Endocrinology.* Oxford: Blackwell, 1992; 113–22

21 Feinsod M, Selhorst JB, Hoyt WF, Wilson CB Monitoring optic nerve function during craniotomy. *J Neurosurg* 1976; **44**: 29–31

22 Foy PM, Chadwick DW, Rajgopalan N, Johnson AL, Shaw MD. Do prophylactic anticonvulsant drugs alter the pattern of seizures after craniotomy? *J Neurol Neurosurg Psychiatry* 1992; **55**: 753–7

23 Goldhill DR, Dalgleish JG, Lake RHN. Respiratory problems and acromegaly. *Anaesthesia* 1982; **37**. 1200–3

24 Goldsack C, Scuplak SM, Smith M. A double-blind comparison of codeine and morphine for postoperative analgesia following intracranial surgery. *Anaesthesia* 1996; **51**: 1029–32

25 Guilleminault C, van den Hoed J. Acromegaly and narcolepsy *Lancet* 1979; **2**: 750–1

26 Guy J, Hindman BJ, Baker KZ *et al.* Comparison of remifentanil and fentanyl in patients undergoing craniotomy for supratentorial space-occupying lesions. *Anesthesiology* 1997; **86**· 514–24

27 Hakala P, Randell T, Valli H. Laryngoscopy and fibreoptic intubation in acromegalic patients. *Br J Anaesth* 1998; **80** 345–7

28 Hassan SZ, Matz GJ, Lawrence AM, Collins PA. Laryngeal stenosis in acromegaly· a possible cause of airway difficulties associated with anesthesia. *Anesth Anal* 1976, **55**: 57–60

29 Hirsch N, Jewkes D *Anaesthesia* for pituitary surgery In: Powell M, Lightman, SL eds. *The Management of Pituitary Tumours a Handbook.* London Churchill Livingstone, 1996; 141–4

30 Johnson MR, Chowdrey HS, Thomas F, Grint C, Lightman SL The pharmokinetics and efficacy of the long-acting somatostatin analogue somatuline in acromegaly *Eur J Endocrinol* 1994; **130** 229–34

31 Johnson M, Lightman SL The medical management of pituitary tumours. In: Powell M, Lightman S. eds *The Management of Pituitary Tumours: a Handbook.* London. Churchill Livingstone, 1996; 39–62

32 Jones TH. The management of hyperprolactinaemia. *Br J Hosp Med* 1995; **53**: 374–8

33 Kelly DF, Laws ER, Fossett D. Delayed hyponatraemia after transsphenoidal surgery for pituitary adenoma. Report of nine cases *J Neurosurg* 1995; **83**· 363–7

34 Kitahata LM. Airway difficulties associated with anaesthesia in acromegaly. *Br J Anaesth* 1971; **43**: 1187–90

35 Lamberts SW, Hofland LJ, de Herder WW, Kwekkeboom DJ, Reubi JC, Krenning EP. Octreotide and related somatostatin analogs in the diagnosis and treatment of pituitary disease and somatostatin receptor scintigraphy. *Front Neuroendocrinol* 1993, **14**· 27–55

36 Leno EM, Tomlinson AA Anaesthesia for supratentorial surgery. current issues. *Curr Anaesth Crit Care* 1997; **8**: 270–4

37 Levy A, Lightman SL. The pathogenesis of pituitary adenomas. *Clin Endocrinol* 1993; **38**: 559–70

38 Levy A, Hall L, Yeudall WA, Lightman SL. p53 gene mutation in pituitary adenomas rare events *Clin Endocrinol* 1994, **41**: 809–14

39 Levy A, Lightman SL. Diagnosis and management of pituitary tumours. *Br Med J* 1994; **308**· 1087–91

40 Levy A, Lightman S. The pathophysiology and pathogenesis of pituitary tumours. In: Powell M, Lightman S eds *The Management of Pituitary Tumours: a Handbook.* London: Churchill Livingstone, 1996 5–29

41 Lightman S, Powell M. The approach to the pituitary patient: an overview In· Powell M, Lightman SL, eds. *The Management of Pituitary Tumours: a Handbook* London: Churchill Livingstone, 1996; 31–7

42 Lolin Y, Jackowski A Hyponatraemia in neurosurgical patients diagnosis using derived parameters of sodium and water homeostasis *Br J Neurosurg* 1992; **6**: 457–66

43 Anon. Management of prolactinoma (editorial). *Lancet* 1990, **336**· 661

44 Matta BF, Menon DK. Management of head injury. part I In

Kaufman L, Ginsberg R, eds. *Anaesthesia Review*. London: Churchill Livingstone, 1997; 163–78

45 Messick JM, Laws ER, Abboud CF. Anesthesia for transsphenoidal surgery of the hypophyseal region. *Anesth Anal* 1978; **57**: 206–15

46 Messick JM, Cucchiara RF, Faust RJ. Airway management in patients with acromegaly. *Anesthesiology* 1982; **56**: 157

47 Moffett AJ Postural instillation: a method of inducing local anaesthesia in the nose. *J Laryngol Otol* 1941; **56**: 429–36

48 Molitch ME. Pregnancy and the hyperprolactinemic woman. *N Engl J Med* 1985; **312**: 1364–70

49 Molitch ME. Management of prolactinomas. *Annu Rev Med* 1989; **40**: 225–32

50 Molitch ME. Pituitary incidentalomas. *Endocrinol Metab Clin North Am* 1997; **26**: 725–40

51 Molitch ME. Pituitary diseases in pregnancy. *Semin Perinatol* 1998; **22**: 457–70

52 Molitch ME. Medical treatment of prolactinomas. *Endocrinol Metab Clin North Am* 1999; **28**: 143–69

53 Mukhtar E, Alexander L, Wilkinson R, Appleton D, Hall R. Thyroid function in acromegaly. *Lancet* 1971; **ii**: 279–83

54 Murrant NJ, Garland DJ. Respiratory problems in acromegaly. *J Laryngol Otol* 1990; **104**: 52–5

55 Murrin KR Intubation procedure and causes of difficult intubation In: Latto IP, Rosen M, eds. *Difficulties in Tracheal Intubation* London: Baillière Tindall, 1985; 75–89

56 Newfield P, Albin MS, Chestnut JS, Maroon J. Air embolism during trans-sphenoidal pituitary operations. *Neurosurgery* 1978; **2**: 39–42

57 Nicholson KEA, Rogers JE. Cocaine and adrenaline paste: a fatal combination? *Br Med J* 1995; **311**: 250–1

58 North JB, Penhall RK, Hanieh A, Hann CS, Challen RG, Frewin DB. Postoperative epilepsy: a double-blind trial of phenytoin after craniotomy. *Lancet* 1980; **i**: 384–6

59 Oldfield EH, Chrousos GP, Schulte HM *et al.* Preoperative lateralization of ACTH-secreting pituitary microadenomas by bilateral. and simultaneous inferior petrosal venous sinus sampling. *N Engl J Med* 1985; **312**: 100–3

60 Ovassapian A. *Fiberoptic Airway Endoscopy in Anesthesia and Critical Care* New York: Raven Press, 1990; 57–79

61 Perks WH, Horrocks PM, Cooper RA *et al.* Sleep apnoea in acromegaly. *Br Med J* 1980; **280**: 894–7

62 Piper JG, Dirks BA, Traynelis VC, VanGilder JC. Perioperative management and surgical outcome of the acromegalic patient with sleep apnea. *Neurosurgery* 1995; **36**: 70–4

63 Powell M, Lightman SL. Post-operative management. In: Powell M, Lightman, eds. *The Management of Pituitary Tumours: a Handbook*. London: Churchill Livingstone, 1996; 145–58

64 Razis PA. Anesthesia for surgery of pituitary tumors. *Int Anesthesiol Clin* 1997; **35**: 23–34

65 Ravussin P, de Tribolet N, Wilder-Smith OHG. Intravenous anaesthesia is the best for neurological surgery. *J Neurosurg Anesthesiol* 1994: **6**; 285–9

66 Robertson GL, Aycinena P, Zerbe RL. Neurogenic disorders of osmoregulation. *Am J Med* 1982; **72**: 339–53

67 Rossi E, Zuppi P, Pennestri F *et al.* Acromegalic cardiomyopathy. Left ventricular filling and hypertrophy in active and surgically treated disease. *Chest* 1992; **102**: 1204–8

68 Shipley JE, Schteingart DE, Tandon DE, Strakman MN. Sleep architecture and sleep apnea in patients with Cushing's disease. *Sleep* 1992; **15**: 514–8

69 Shung J, Avidan S, Ing R, Klein DC, Pott L. Awake intubation of the difficult airway with the intubating laryngeal mask airway. *Anaesthesia* 1998; **53**: 645–9

70 Smith I, Nathanson M, White PF. Sevoflurane—a long awaited volatile anaesthetic. *Br J Anaesth* 1996; **76**; 435–45

71 Soule SG, Jacobs HS. The evaluation and management of subclinical pituitary disease. *Postgrad Med J* 1996; **72**: 258–62

72 Southwick JP, Katz J. Unusual airway obstruction in the acromegalic patient-indications for tracheostomy. *Anesthesiology* 1979; **51**: 72–3

73 Stoneham MD, Cooper R, Quiney NF, Walters FJ. Pain following craniotomy: a preliminary study comparing PCA morphine with intramuscular codeine phosphate. *Anaesthesia* 1996; **51**: 1176–8

74 Sugihara N, Shimizu M, Kita Y *et al.* Cardiac characteristics and postoperative courses in Cushing's syndrome. *Am J Cardiol* 1992; **69**: 1475–80

75 Todd MM, Warner DS, Sokoll MD *et al* A prospective, comparative trial of three anesthetics for elective supratentorial craniotomy. Propofol/fentanyl, isoflurane/nitrous oxide, and fentanyl/nitrous oxide. *Anesthesiology* 1993; **78**: 1005–20

76 Van Aken H. Anaesthetic agents: total intravenous and inhalational anaesthesia. In: Van Aken H, ed. *Neuroanaesthetic Practice*. London: BMJ Publishing Group, 1995: 91–132

77 Warner DS, Hindman BJ, Todd MM *et al.* Intracranial pressure and hemodynamic effects of remifentanil versus alfentanil in patients undergoing supratentorial craniotomy. *Anesth Analg* 1996; **83**: 348–53

78 Weglinski MR, Perkins WJ. Inhalational versus total intravenous anaesthesia for neurosurgery: theory guides, outcome decides. *J Neurosurg Anesthesiol* 1994; **6**: 290–3

79 Williams RG, Richards SH, Mills RG, Eccles R. Voice changes in acromegaly. *Laryngoscope* 1994; **104**: 484–7

80 Wilson CB. Role of surgery in the management of pituitary tumours. *Neurosurg Clin N Am* 1990; **1**: 139–59

81 Wright AD, Hill DM, Lowy C, Russell Fraser TR. Mortality in acromegaly. *Q J Med* 1980; **280**: 1–16

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Thyroid disease

P. A. Farling

Department of Anaesthetics, Royal Victoria Hospital, Belfast BT12 6BA, UK

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Disease of the thyroid gland is common. For example, in endemic areas, the incidence of goitre is 15–30% of the adult population.[66] Most anaesthetists, although their practice may not include endocrine surgery, will frequently be required to manage patients with thyroid disease. Thyroid diseases that have anaesthetic implications include hypothyroidism, hyperthyroidism and conditions requiring thyroidectomy. Those presenting with well-controlled hypo- and hyperthyroidism do not present much difficulty for the anaesthetist However, patients with uncontrolled myxoedema, or those with uncontrolled hyperthyroidism presenting as an emergency, are at considerable risk.[42] Anaesthesia for thyroidectomy may be complicated by airway problems such as retrosternal extension of the gland. The anaesthetist should, therefore, pay particular attention to preoperative assessment of the airway and should be able to deal with acute airway complications in the perioperative phase.

History

In his book entitled *The History of Endocrine Surgery*, Richard Welbourn details the beginnings of thyroidectomy.[99] Goitres were recognized in antiquity and were described in Chinese literature in 2700 BC. Since they were never endemic around the Mediterranean, there was no mention of goitre in Egyptian or Greek writings. In the twelfth and thirteenth centuries, the school of Salerno in Italy was the cradle of thyroid surgery. At that time goitres were removed using horrific-sounding instruments such as setons, hot irons, stypics and asphodel powder. The American surgeon William Halsted could trace accounts of only eight operations in which the scalpel was used between 1596 and 1800. During one of these procedures, described by Fabricius in 1646, the patient, a 10-yr-old girl, died on the table and the surgeon was gaoled! In 1821, Hedenus reported the successful removal of six suffocating goitres by dissection and ligation of all the arteries. Needless to say, these operations were prone to complications which were often fatal and, in 1850, the French Academy of Medicine condemned operations on the thyroid gland. However, the advances of anaesthesia, antisepsis and haemostasis allowed surgeons, such as Billroth of Vienna and Kocher of Berne, to perform many more thyroid operations with reduced mortality. In 1849, Nikolai Pirogoff of St Petersburg was the first to use general anaesthesia for a thyroid operation. He used ether on a girl of 17 yr whose goitre was causing tracheal compression.[99]

Thomas Peel Dunhill performed his first thyroidectomy in 1907 under local anaesthetic [94] He developed surgery as an effective and safe treatment for thyrotoxicosis and in 1911 presented his series of 230 cases of exophthalmic goitre, which included only four deaths. Other notable thyroid surgeons included Charles Mayo and George Crile.

In the UK, Stanley Rowbotham was a pioneer of anaesthesia for thyroid surgery;[18] with his surgeon Cecil Joll, he performed 946 goitre operations between 1941 and 1944. Although these operations were performed before the introduction of antithyroid drugs, by Astwood in 1943,[7] there were only nine deaths in the series. Rowbotham combined local analgesia with light general anaesthesia and even contrived, at the request of the surgeon, to get the patient to strain when the haemostatic sutures were in place. He used one breath of ether to accomplish this manoeuvre.[76]

Patients with thyroid disease scheduled for non-thyroid surgery

Hypothyroidism

The incidence of hypothyroidism depends on the level of iodide in the diet.[66] The prevalence of overt hypothyroidism in iodine-sufficient areas is five per 1000 and that for the subclinical form is 15 per 1000.[55] Hypothyroidism may result in depression of myocardial function, decreased spontaneous ventilation, abnormal baroreceptor function, reduced plasma volume, anaemia,[82] hypoglycaemia, hyponatraemia and impaired hepatic drug metabolism.[67] Hypothyroid patients should be rendered euthyroid before

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surgery[42] and, as with other types of endocrine surgery, close communication with the metabolic physicians is advised. It should be remembered that, because thyroxine (T4) has a half-life of 7 days, it will not have an effect for some time after administration. The half-life of tri-iodothyronine (T3) is 1.5 days. The combination of intravenous T3 and T4 is recommended in the management of preoperative myxoedematous coma, which is an extremely rare occurrence. Careful administration is essential, particularly in the elderly, as angina may be precipitated.[60]

There is some debate about whether or not surgery should be postponed in a mild or subclinical hypothyroid patient.[10] It is logical to avoid premedication in overtly hypothyroid patients and to use regional anaesthesia wherever possible. T4 may be omitted on the morning of surgery but it is advisable to give the patient's usual morning dose of T3. The presence of a hypometabolic state necessitates careful perioperative cardiovascular monitoring and judicious use of anaesthetic drugs.

Preventative measures should be adopted to protect against hypothermia. Because of an increased incidence of adrenocortical insufficiency and a reduced adrenocorticotropic hormone response to stress, hypothyroid patients should receive hydrocortisone cover during periods of increased surgical stress.[67] There are several reports of severe cardiovascular and respiratory depression in hypothyroid patients during general anaesthesia. Hypothyroidism should therefore be considered in any obese, debilitated patient who displays perioperative cardiovascular or respiratory instability.[54]

Hyperthyroidism

Thyrotoxicosis affects approximately 2% of women and 0.2% of men in the general population.[27] The prevalence of overt hyperthyroidism in iodine-sufficient areas is two per 1000 and that of subclinical hyperthyroidism is six per 1000.[55] The classical features of thyrotoxicosis are well known and include hyperactivity, weight loss and tremor. Of importance to the anaesthetist are the cardiovascular effects of hyperthyroidism including atrial fibrillation, congestive cardiac failure and ischaemic heart disease.[44] Thrombocytopaenia may be associated with thyrotoxicosis.[82] General anaesthesia should be considered as the method of choice for patients with exophthalmos requiring eye surgery.[17]

In an attempt to prevent the dreaded complication of 'thyroid storm', patients should be euthyroid before surgery.[42 86] This is achieved by the use of antithyroid drugs, commonly carbimazole or propylthiouracil. These drugs block the synthesis of thyroxine but take 6–8 weeks to work. Beta-blockers, particularly propranolol, are used to ameliorate the effects of thyrotoxicosis[13] and are effective in the acute preoperative phase. Longer-acting beta-blockers such as atenolol or nadolol may achieve better control of symptoms.[27 36] Anaesthetic drugs may be affected by the hypermetabolic state of hyperthyroidism. For example, the clearance and distribution volume of propofol are increased in hyperthyroid patients. When total intravenous anaesthesia is used, propofol infusion rates should be increased to reach anaesthetic blood concentrations.[91]

Thyroid crisis

The hypermetabolic crisis known as 'thyroid storm' is frequently mentioned in textbooks of anaesthesia[72] but is now rarely seen because of the widespread use of antithyroid drugs, such as carbimazole, and beta-blockers. However, thyroid crisis still occurs in uncontrolled hyperthyroid patients as a result of a trigger such as surgery, infection or trauma. Pugh and colleagues described a case following Caesarean section[73] and Naito and colleagues described a tragic case resulting from active metastatic thyroid carcinoma in a severely burned patient.[68] Supportive management of thyroid crisis includes hydration, cooling, inotropes and, formerly, steroids. Beta-blockade, using propranolol, and antithyroid drugs are used as the first-line of treatment. Esmolol was successful in treating a child of 14 months who developed a thyroid crisis 3 h after thyroidectomy.[47] An 85-yr-old with multinodular goitre and severe thyrotoxicosis was also managed with esmolol.[95] However, it should be noted that thyroid crisis has been reported during beta-blockade.[85] An acute thyroid crisis on induction of anaesthesia, which was mistakenly diagnosed as malignant hyperthermia, was treated successfully by boluses of dantrolene 1 mg kg^{-1}.[9] Christensen and Nissen reported the successful use of dantrolene to treat thyroid crisis in a child who had not responded to traditional measures.[16] Since thyroid hormones sensitize the adrenergic receptors to endogenous catecholamines, magnesium sulphate would seem to be, theoretically, a useful drug. Magnesium reduces the incidence and severity of dysrhythmias caused by catecholamines (James MFM, personal communication).

Thyroidectomy

The indications for thyroidectomy include: proven or suspected thyroid malignancy; obstructive symptoms; retrosternal goitre, even in the absence of obstruction; hyperthyroidism that is unresponsive to medical management; recurrent hyperthyroidism; cosmetic reasons; anxiety (patients with a small goitre may insist on having it removed); patients with Hashimoto's disease, goitre and hypothyroidism usually respond to thyroxine therapy, but thyroidectomy would be indicated if there is any suspicion of superimposed lymphoma.[90]

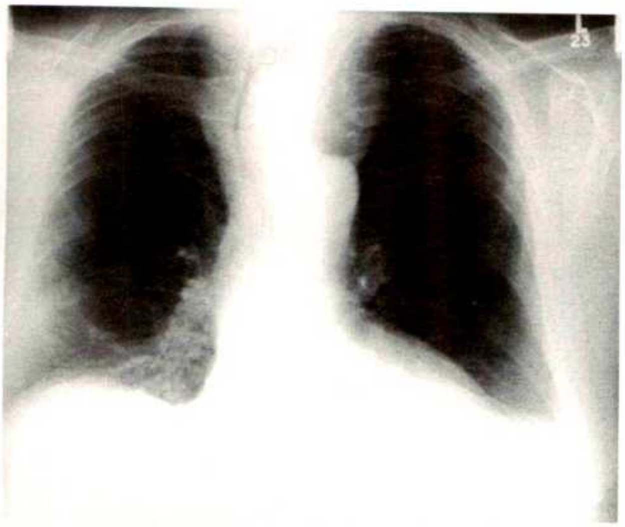

Fig 1 Chest x-ray showing gross tracheal compression and deviation by a retrosternal goitre.

Preoperative assessment

General history taking and examination of patients scheduled for thyroidectomy should include identification of abnormalities of thyroid function. Besides symptoms and signs of hypo- and hyperthyroidism, evidence of other medical conditions should be sought, particularly cardiorespiratory disease and associated endocrine disorders. For example, patients who require thyroidectomy for medullary cancer may have an associated phaeochromocytoma.[101]

Problems with airway management will be the main concern of the anaesthetist when confronted by a patient with a goitre. The patient may give a history of respiratory difficulties, for example positional dyspnoea, and this may be associated with a degree of dysphagia. As described later, patients with retrosternal goitre may exhibit signs of vena caval obstruction. Other assessments of the airway will include assessment of distances between incisors, the thyromental distance, the degree of protrusion of the lower teeth, head and neck mobility and observation of pharyngeal structures.[75]

Routine investigations include thyroid function tests, haemoglobin, white cell and platelet count, urea and electrolytes, including serum calcium, chest x-ray and indirect laryngoscopy. Patients may have had fine needle aspiration as a diagnostic test in the out-patient clinic. An ENT colleague routinely performs indirect laryngoscopy in order to document any preoperative vocal cord dysfunction.[77] This investigation is useful to the anaesthetist since the need for a fibreoptic instrument to view the vocal cords, if indirect laryngoscopy is unsuccessful, will alert the anaesthetist to the probability of a difficult intubation.

A chest x-ray (Fig. 1) is requested to seek evidence of tracheal compression and deviation and lateral thoracic inlet views have traditionally been used to show tracheal compression in the antero-posterior plane (Fig. 2).

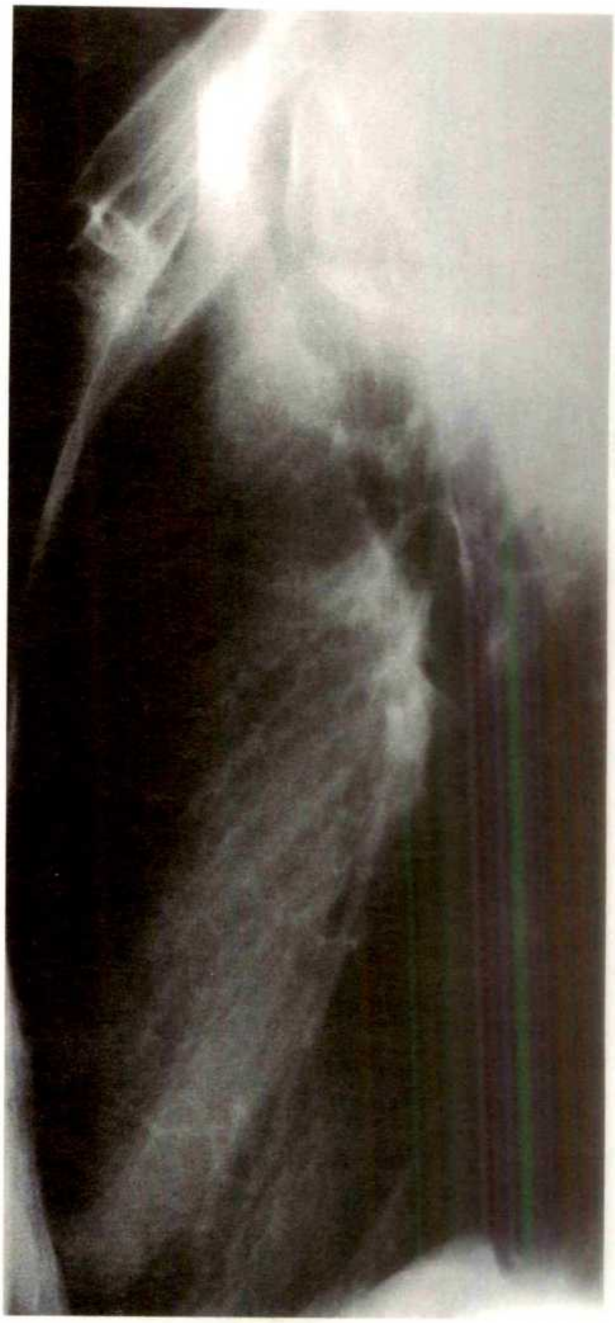

Fig 2 Lateral thoracic inlet x-ray showing tracheal compression antero-posteriorly.

Other investigations, while not routine, will be of value in certain cases. Computerized tomography (CT) can provide excellent views of retrosternal goitres[8] (Fig. 3): compare the reconstructed CT scan in Fig. 4 with the chest x-ray of the same patient (Fig. 1).

Magnetic resonance imaging (MRI) has the advantage of providing images in the sagittal and coronal planes, as well as transverse views[28] (Figs 5–7). The coronal view of this patient (Fig. 6) indicated that it would not be possible to see

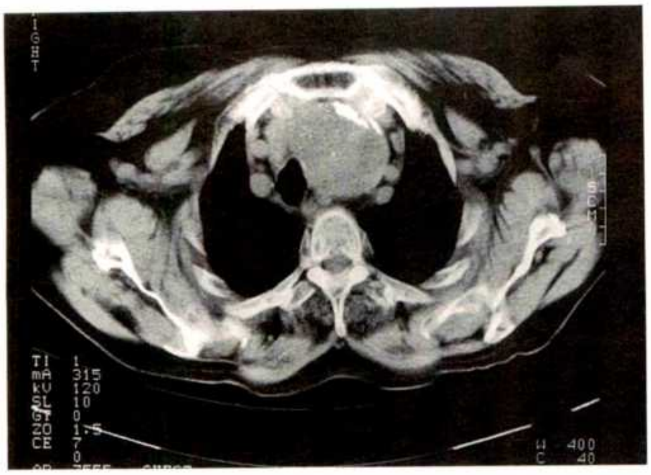

Fig 3 CT scan of retrosternal goitre.

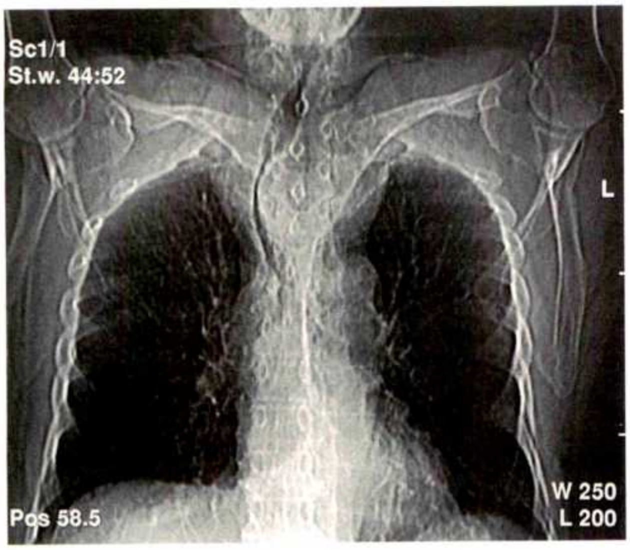

Fig 4 Reconstructed CT scan.

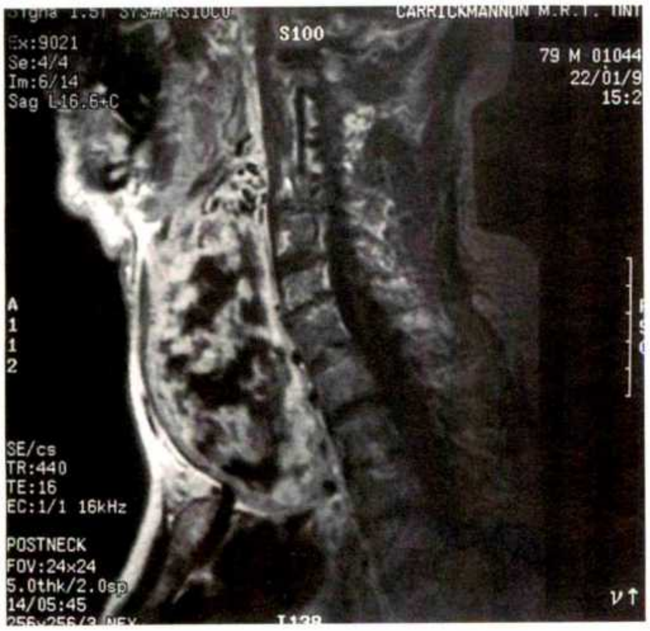

Fig 5 Sagittal MRI scan of goitre.

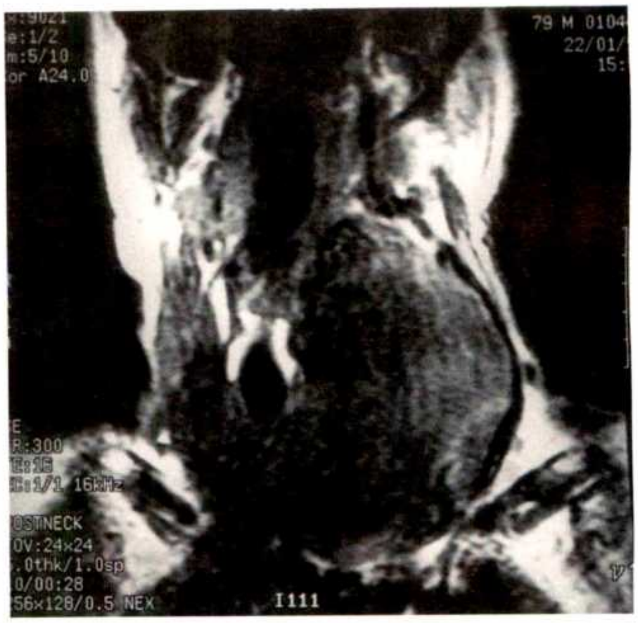

Fig 6 Coronal MRI scan of goitre.

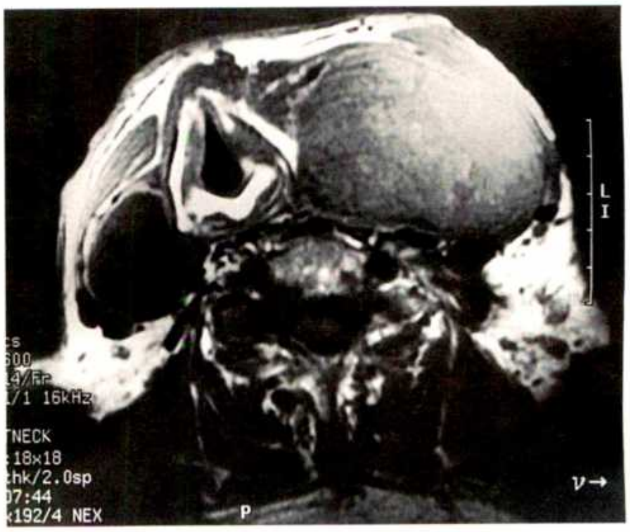

Fig 7 Transverse MRI scan of goitre.

the larynx by direct laryngoscopy and so fibreoptic intubation was planned.

The usefulness of respiratory function tests is debatable. Respiratory flow volume loops showed upper airway obstruction in 33% of 153 consecutive patients presenting with thyroid enlargement. This was unrelated to the type or size of goitre.[33]

Following a careful history and examination and with the assistance of a number of investigations, the anaesthetist can be in a position to discuss with the patient the various options for airway management. These options will include straightforward intravenous induction with tracheal intubation, inhalational induction or fibreoptic intubation. The patient should be warned what to expect postoperatively and an anxiolytic premedication prescribed.

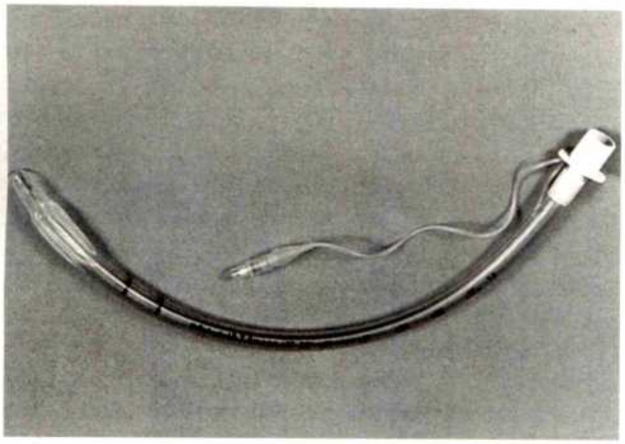

Fig 8 Armoured tracheal tube.

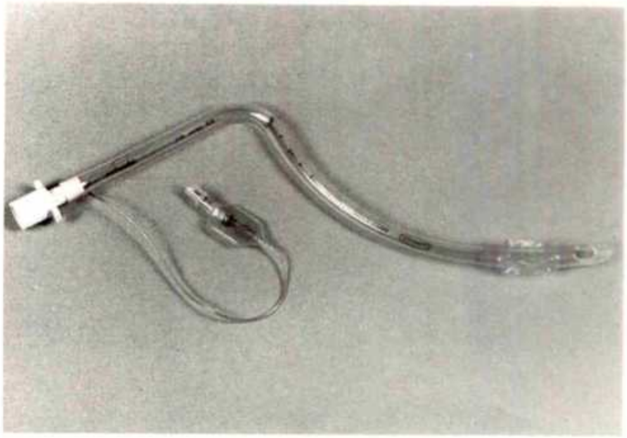

Fig 9 'North-polar' tracheal tube.

Anaesthetic technique

Regional anaesthesia

It is possible to perform thyroidectomy under bilateral deep or superficial cervical plexus blocks.[50] There are, however, a number of complications of this technique, including vertebral artery puncture, epidural subarachnoid spread and bilateral phrenic nerve block. Regional anaesthesia is a useful alternative for particular circumstances, for example, thyroidectomy for amiodarone-induced hyperthyroidism.[46] Thyroidectomy under regional anaesthesia is not routinely practised in the UK.

In some parts of the world, thyroidectomy is performed under acupuncture, with or without supplementary analgesics.[45] Hypnosedation, a combination of hypnosis and light conscious sedation, has been suggested for endocrine surgery including thyroidectomy.[64]

General anaesthesia

General anaesthesia with tracheal intubation and muscle relaxation is the most popular anaesthetic technique for thyroidectomy. The laryngeal mask airway (LMA†)[14] has been used with spontaneous respiration and intermittent positive pressure ventilation in thyroid surgery.[34 38 88] This technique requires close co-operation between surgeon and anaesthetist. Relative contraindications to the use of the LMA include tracheal narrowing and/or deviation.

As described in the section on postoperative complications, use of the LMA allows vocal cord movement to be seen via a fibreoptic laryngoscope when the recurrent laryngeal nerve is stimulated.[88] However, there is a risk that the LMA will be displaced during surgery and laryngospasm occurs in relation to surgical manipulation.[15] Use of the intubating laryngeal mask in a patient with a large goitre proved difficult because of deviation of the laryngeal inlet.[96]

Induction of anaesthesia for routine thyroidectomy, when no difficulty with intubation is expected, is straightforward. The trachea is intubated usually using conventional laryngoscopy. The tracheal tube should not kink when it attains body temperature during prolonged surgery, so a reinforced tube should be considered (Fig. 8). 'North-polar' oral tracheal tubes (Fig. 9) are an alternative as they keep the respiratory filter away from the surgical field. Nasal tracheal tubes may also be used although vasoconstriction will be required to prevent epistaxis. It is wise to select a small reinforced tracheal tube if there is any degree of tracheal compression.

Unexpected difficult intubation

Occasionally, even though no difficulty has been predicted, the larynx is not easily seen, so the anaesthetic team must be experienced and prepared to cope with an unexpected difficult intubation. Items which should be available to deal with such a situation include: various sizes of tracheal tubes; gum elastic bougies; a levering laryngoscope;[61] straight-bladed laryngoscopes; an LMA;[14] ready access to an intubating fibrescope; and some means of trans-tracheal ventilation.

Expected difficult intubation

If preoperative airway assessment and/or the inability of the ENT surgeon to see the vocal cords by indirect laryngoscopy have predicted any difficulty with intubation, then the anaesthetist must have a clear strategy for intubation. The anaesthetist should expect that 6% of tracheal intubations for thyroid surgery will be difficult.[51] It has been reported that the ease of intubation was unrelated to the extent of abnormality seen on imaging studies of the neck.[62] Whenever there is concern that the airway will be lost if anaesthesia is induced, awake fibreoptic intubation is the method of choice. The traditional technique of inhalational induction has regained acceptability following the introduction of sevoflurane.[57 98] It may be adopted when the

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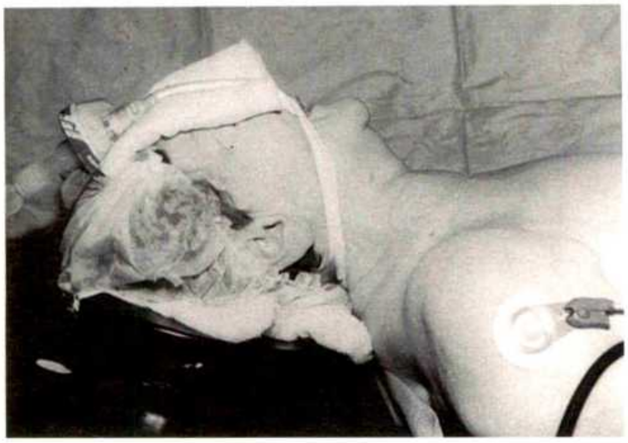

Fig 10 Patient position.

patient is extremely anxious about awake intubation, and the anaesthetist believes that the size of the goitre will not cause the airway to be lost after induction of anaesthesia.

Positioning the patient

After intubation, by whatever means, the position of the tracheal tube is checked, the tube is secured and the patient's eyes are protected. These practical points are important as the use of head towels prevents the anaesthetist from inspecting the patient's face during the procedure. Particular care should be taken when the patient suffers from exophthalmos.

The patient is positioned with a sandbag between the shoulder blades and the head resting on a padded 'horseshoe' or Whitlock headrest[100] (Fig. 10). Both arms are placed by the side, as the surgeon will need to stand on either side of the patient. A long connector for the i.v. infusion allows access from the foot of the bed. A 25° upward tilt of the head will assist venous drainage, although this should be performed with careful attention to arterial pressure, particularly in patients who have been receiving beta-blockers. Finally, slight head extension will allow the surgeon excellent access to the thyroid gland.

Surgical technique

The skin is infiltrated with 10–20 ml of 0.5% bupivacaine and epinephrine 1:200 000. Skin flaps are raised and the strap muscles separated in the midline. It is rarely necessary to divide the strap muscles. The upper pole is mobilized and the superior thyroid vessels ligated. Mobilization of the lobe is completed and the parathyroid glands and recurrent laryngeal nerve are identified routinely and protected during dissection of the thyroid from the trachea. Haemostasis is secured and the strap muscles and platysmal layers apposed. The skin is closed with staples.[30]

Postoperative care

Residual neuromuscular block is reversed and the patient is allowed to recover from anaesthesia. If there has been any concern during dissection of the recurrent laryngeal nerve, the vocal cords are checked and the surgeon reassured. A fibreoptic endoscope may be used to view the vocal cords atraumatically.[59] When adequate spontaneous respiration and laryngeal reflexes have returned, the patient is extubated. Every attempt should be made to prevent coughing,[32 40 49 63] although recent chest infection[69] or a history of cigarette smoking[22] may make this difficult. If there is no immediate respiratory obstruction, the patient is transferred to the recovery ward. The patient is carefully observed for the development of a cervical haematoma and is returned to the ward after attaining appropriate discharge criteria. Signs of hypocalcaemia are treated by calcium supplements and, following total thyroidectomy, thyroxine 100 μg daily is prescribed. Postoperatively, vocal cord function is examined by indirect laryngoscopy before discharge. The new technique of video laryngostroboscopy is an accurate means of diagnosing vocal abnormalities after thyroidectomy, although it may not be cost-effective.[48]

Thyroidectomy in special situations

Hyperthyroidism

Thyroidectomy is offered to patients with autoimmune hyperthyroidism (Graves' disease) when medical treatment proves inadequate. Patients should be euthyroid before surgery. Approximately three patients per 1000 are unable to take antithyroid drugs because of serious adverse reactions, the most severe of which include agranulocytosis, hepatitis, aplastic anaemia and lupus-like syndromes.[27] The clinical manifestations of thyrotoxicosis are usually controlled by beta-blockers and it has been suggested that beta-blockers alone may be adequate preparation for thyroidectomy.[36] Traditionally, Lugol's iodine has been given for 10 days preoperatively, in a dose of 0.5 ml three times a day, to reduce bleeding, as antithyroid drugs make the thyroid more vascular. Although this contention was supported by measuring thyroid blood flow using uptake of a radioisotope of thallium,[58] many surgeons have abandoned this practice. This is because the thyroid gland is now usually dissected without transection.

Huge goitres

Endemic goitre still exists in many parts of the world.[87] Huge nodular goitres can occur, with a neck circumference of about 60 cm (Fig. 11). The specimen from this patient weighed 700 g (Fig. 12). While these goitres may have a dramatic appearance, they often present fewer problems than smaller retrosternal goitres.[39] The problems associated with huge goitres include difficult intubation (although lifting the goitre anteriorly usually relieves airway obstruction), large blood loss, prolonged operating time and postoperative tracheomalacia.[80 87] Blood loss is less of a problem when the surgeon dissects the thyroid without transecting it, as shown in Fig. 12. Use of a small armoured

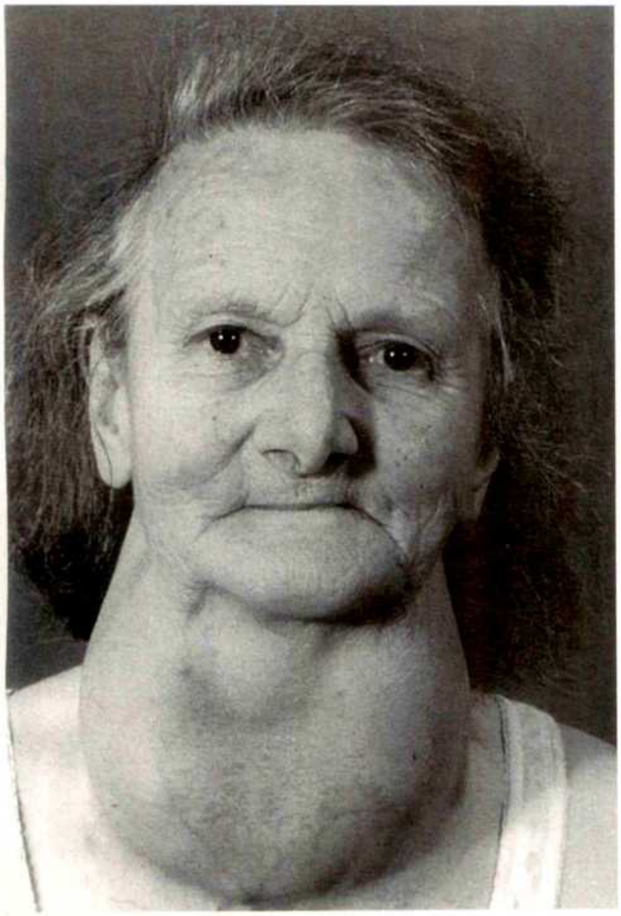

Fig 11 Patient with large goitre.

tracheal tube is recommended to negotiate the compressed and deviated trachea. An armoured tracheal tube is less likely to kink during surgical manipulation, while unarmoured tubes may soften during these prolonged procedures.

Retrosternal goitre

Retrosternal enlargement of the thyroid can be asymptomatic[71] but usually causes compression of mediastinal structures (Fig. 4). Dyspnoea, choking and hoarseness may occur. Dysphagia is the most common oesophageal symptom but a case has been reported where bleeding from varices was the first presentation of a retrosternal goitre.[4] Superior vena caval syndome can occur and may be complicated by thrombosis.[78] Retrosternal goitres may also cause cerebral hypoperfusion as a result of arterial compression and thyrocervical steal, phrenic and recurrent laryngeal nerve palsies, Horner's syndrome, pleural effusions, chylothorax and pericardial effusions.[4]

Although some retrosternal goitres are large, the vast majority can be removed by the cervical route.[71] As the surgeon manipulates the retrosternal gland, compression of the trachea can be worsened. During excision of the retrosternal goitre shown in Fig. 13, obstructive symptoms were relieved when a retrosternal cyst within the goitre ruptured. Of 21 patients requiring surgery for acute, life-threatening airway obstruction resulting from goitre, only one required sternotomy.[79] Since parathyroid surgery also occasionally requires mediastinal exploration, the endocrine theatre team should be able to perform sternotomy. Dissection in the neck may stimulate the carotid sinus and this, coupled with median sternotomy, can produce profound vagal stimulation leading to bradycardia and even sinus arrest. Tracheal deviation and compression resolve immediately after excision of the goitre, but tracheomalacia should be anticipated when the patient has complained of a goitre of longstanding. Figure 14 shows the appearance immediately postoperatively of the patient in Figs 1 and 4. Note that some tracheal dilation remained above the site of the original compression.

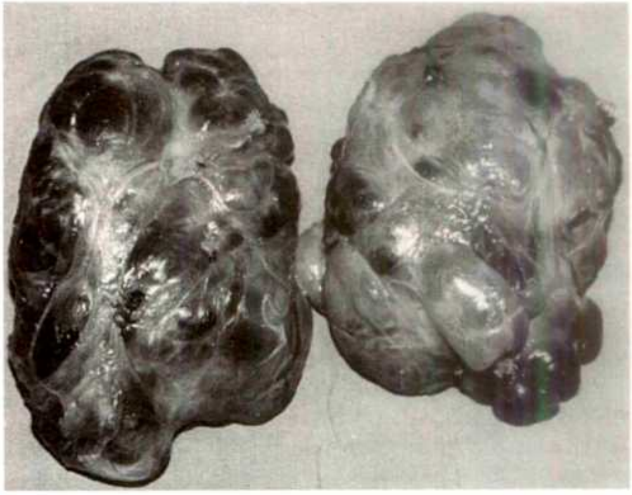

Fig 12 Specimen of large goitre; width 15 cm, weight 700 g.

Thyroid cancer

When thyroidectomy is performed for removal of a thyroid cancer, there is potentially a greater risk of damage to the recurrent laryngeal nerve.[89] Medullary carcinoma may be associated with phaeochromocytoma in patients with multiple endocrine neoplasia (MEN) type 2[101] (see 'Hormones and the gut' by Holdcroft, this issue). Medullary and papillary carcinoma spread to local lymph nodes and may require block dissection of the neck. These tumours may involve surrounding tissue, for example, muscle. Follicuclar carcinoma spreads via the blood to lungs and bone, and metastases can produce thyroxine.[68] Lymphoma is diagnosed by fine needle aspiration or core biopsy and is usually treated by radiotherapy. Anaplastic carcinoma is extremely malignant and usually only palliative radiotherapy is indicated.

Rarely is a patient's condition allowed to progress to severe respiratory distress before surgical intervention is

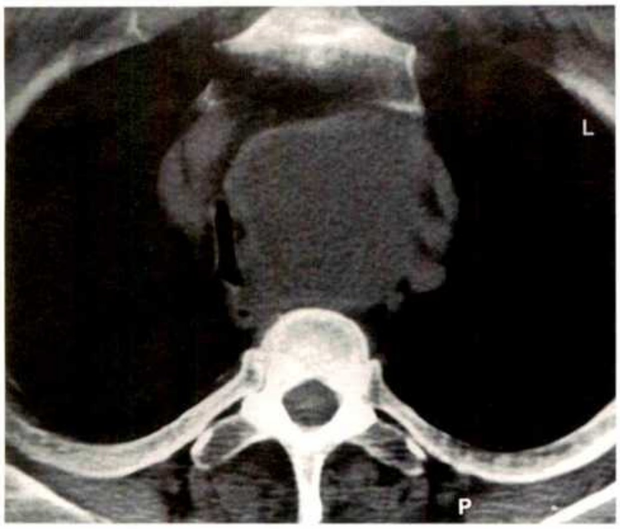

Fig 13 Retrosternal goitre with severe tracheal compression.

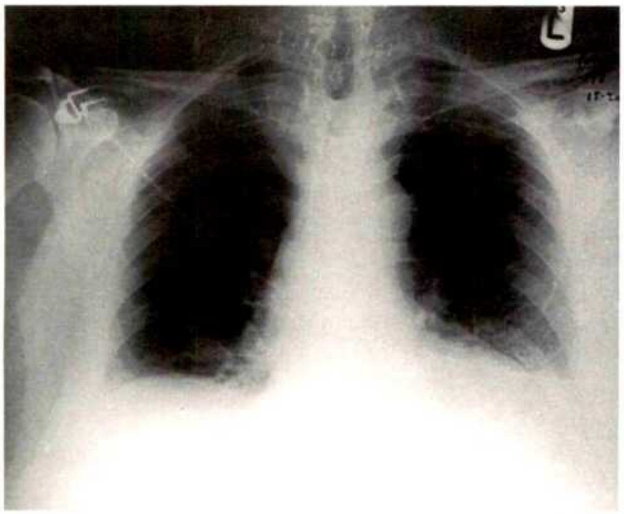

Fig 14 Post-operative chest x-ray showing immediate recovery of tracheal position.

recommended. Percutaneous dilatational tracheostomy has been performed to relieve severe airway obstruction as a palliative measure.[1] A large neglected thyroid lymphoma with associated supraglottic oedema was managed by controlled tracheotomy following femoro-femoral cardiopulmonary bypass that had been initiated under local anaesthetic. This is described as the ultimate solution to the problem of a difficult airway![11]

Multiple endocrine neoplasia

Patients with MEN2 are at risk of early medullary thyroid cancer. Prophylactic thyroidectomy is advocated in children of MEN2 families, who are shown by genetic screening to carry a mutation of a proto-oncogene. Children with MEN2B should have thyroidectomy in the first year of life.[5 92] I have anaesthetized two siblings, aged 10 yr and 8 yr, for prophylactic thyroidectomy. Histopathology revealed islands of pre-malignant cells in the specimen from the younger child.

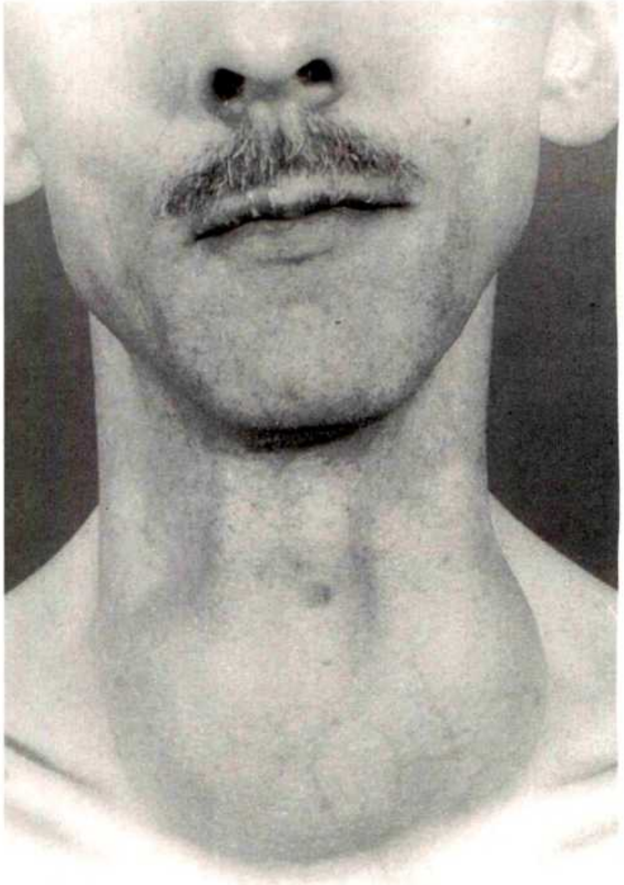

Fig 15 Patient with medium sized goitre.

Lingual thyroid

Embryologically, the thyroid grows from the third and fourth branchial arch and descends from the foramen caecum towards the neck. If its development is arrested, a lingual thyroid may result. This can be diagnosed by thallium or technetium scan and should be treated with respect, as it may be the patient's only thyroid tissue. Furthermore, it may bleed excessively if biopsy is attempted. The presence of a lingual thyroid should alert the anaesthetist to a potential difficult intubation.[26]

Concomitant disease

Patients who require thyroidectomy may have other unrelated diseases that affect their anaesthetic management. Figures 15 and 16 show a patient with a medium sized goitre and minimal neck extension. His chest x-ray (Fig. 17)

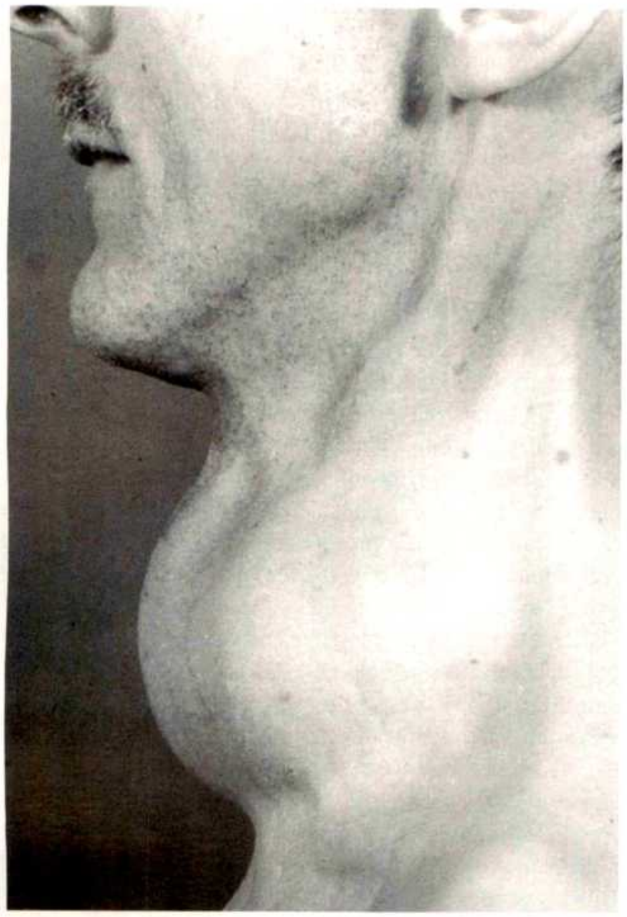

Fig 16 Minimal neck extension.

confirmed the clinical impression of tracheal deviation. Careful inspection of the chest x-ray and the lateral x-ray of his cervical spine (Fig. 18) show the reason for the poor neck extension. This patient had severe ankylosing spondylitis but tracheal intubation was performed relatively easily by the awake fibreoptic technique.[25]

Postoperative complications

As complications often occur during procedures for recurrent goitre, it is important to eliminate the former practice of 'partial thyroidectomy'. When total thyroidectomy is not indicated then, at least, total thyroid lobectomy should be performed.

Extubation problems

In general the incidence of respiratory complications at tracheal extubation and in the recovery room is greater than that at intubation.[6] These complications include coughing, oxygen desaturation, laryngospasm and respiratory obstruction. Coughing at extubation should be avoided, but this is often difficult to achieve, particularly if the patient has irritable airways because of smoking[22] or recent respiratory tract infection.[69] Upper airway reflex sensitivity decreases with increasing age.[23] Possible preventive interventions include extubation during relatively deep anaesthesia, administration of intravenous narcotics, for example alfentanil[63] and lidocaine. Lidocaine may be administered intravenously[32] or topically,[49] or even prestored in the cuff of the tracheal tube.[40]

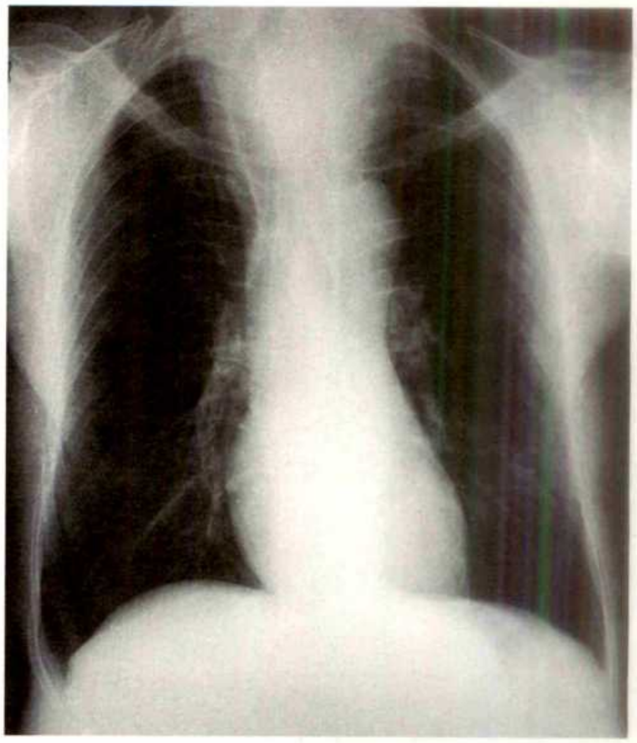

Fig 17 Chest x-ray of patient in Fig. 15 showing tracheal compression and rigid thoracic spine.

Haematoma

Postoperative haemorrhage is potentially catastrophic when one is operating on the neck, but can be avoided by meticulous haemostasis. The anaesthetist may be asked to maintain the patient's intrathoracic pressure positive for 10–20 s in order to assess haemostasis before wound closure.[74] Recovery ward staff should be experienced at observing the early signs of haematoma formation so that both the surgeon and anaesthetist can be alerted. Traditionally, clip removers were kept at the bedside to enable rapid relief of a haematoma. If it is necessary to re-open the incision to relieve compression of the airway, then it is essential to open all layers.

Repeat surgery for haemorrhage is rare (0.36% of 3008 cases).[51] Prompt decision-making is important and early re-intubation is recommended. The anaesthetic team should be aware of the problems involved in the induction of anaesthesia in a patient for cervical re-exploration. Obviously, the later the intubation is performed, the more difficult it becomes as the haematoma expands and compresses the airway.

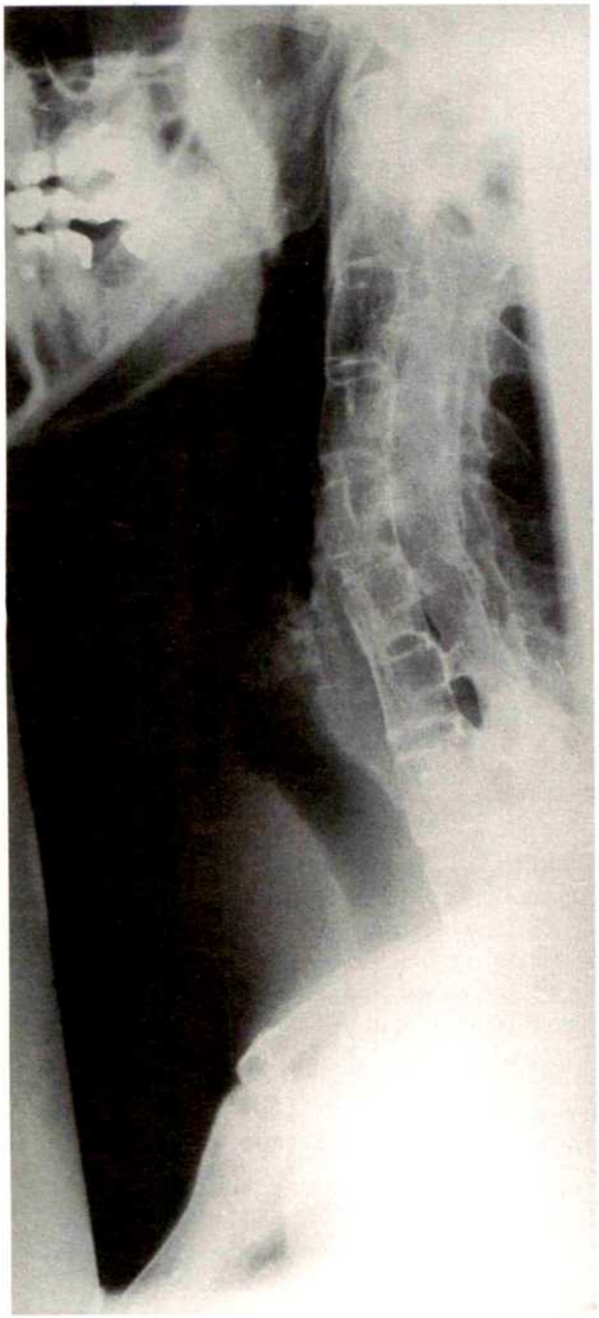

Fig 18 Lateral cervical spine x-ray of patient in Fig. 15 showing typical 'bamboo spine' of ankylosing spondylitis.

Respiratory obstruction may be caused by laryngeal and pharyngeal oedema as a result of venous and lymphatic obstruction by the haematoma, rather than direct tracheal compression. Early re-intubation rather than precipitous re-opening of the incision is the best way to manage this complication (James MFM, personal communication).

Recurrent laryngeal nerve damage

Good operating technique with routine identification of the recurrent laryngeal nerve greatly minimizes accidental nerve injury.[37] Injury to the recurrent laryngeal nerve can occur by a number of mechanisms, including ischaemia, contusion, traction, entrapment and actual transection. The incidence of temporary unilateral vocal cord paralysis resulting from damage to the recurrent laryngeal nerve is 3–4%.[30] Permanent unilateral vocal cord paralysis occurs in <1% of patients[51] and bilateral vocal cord paralysis should be extremely rare. There is a greater risk of nerve damage during surgery for malignancy[89] and secondary operations. Anatomical variability[70] and distortions will increase the risk of nerve injury, particularly when the surgeon is inexperienced.

The surgeon may seek reassurance by asking the anaesthetist to observe the movement of the vocal cords at the end of surgery. This may prove difficult as the patient is emerging from the anaesthetic. Rather than using a Mackintosh laryngoscope, vocal cords may be observed using a fibrescope.[59] The LMA may be used to maintain the airway during this procedure.

Attempts to protect the recurrent laryngeal nerve during thyroidectomy have involved detecting vocal cord movement after stimulation of the nerve. Vocal cord adduction causes pressure changes in the inflatable cuff of a tracheal tube placed between the cords.[19] A fibreoptic bronchoscope can be used to observe the vocal cords via an LMA during surgery.[88] Intraoperative electro-physiological monitoring has been performed[21] using a tracheal tube with integrated EMG electrodes positioned at the level of the vocal cords. Succinylcholine is used to intubate the trachea and no further muscle relaxant is used. When the recurrent laryngeal nerve has been identified, the nerve is stimulated with a current of 0.1 mA, increasing in 0.05 mA steps, until an evoked EMG is obtained. While it is unlikely that nerve stimulation will become routine for all thyroidectomies, it may be a useful technique when identification of the recurrent laryngeal nerve is expected to be difficult. However, it is expensive, time-consuming, requires the patient to breathe spontaneously and false-negative responses may occur. Some surgeons are concerned about the effects of repeated nerve stimulation.

Bilateral vocal cord paralysis will lead to stridor at tracheal extubation. Re-intubation will be required and tracheostomy should be considered. Unilateral vocal cord paralysis leads to glottic incompetence, hoarseness, breathlessness, ineffective cough and aspiration. Traditional treatments of vocal cord paralysis include intracordal injection, laryngeal framework surgery, thyroplasty and laryngeal re-innervation. Endolaryngeal vocal cord laterofixation[43] and transcutaneous intracordal silicon injection have been described.[41]

Tracheomalacia

Tracheal collapse following thyroidectomy results from prolonged compression of the trachea by a large, neglected goitre, particularly within the confines of the thoracic inlet.[31] The incidence of tracheomalacia will depend on the frequency of this type of goitre. In a prospective study of 103 patients in Khartoum, five patients required tracheostomy for tracheomalacia.[2] It is a life-threatening complication,[35] which should be considered before extubation, and management strategies should be available. The absence of a leak around the deflated cuff of the tracheal tube should alert the anaesthetist to the possibility of tracheomalacia. After intubation, Sinha and colleagues measure the volume of air required to inflate the cuff of the tracheal tube so that an airtight seal is produced. A similar test is performed at the end of the procedure and tracheomalacia can be detected if there is any decrease in the volume required to inflate the cuff to an airtight seal at the end of the procedure.[83]

Management of tracheomalacia requires urgent re-intubation, possibly tracheostomy and some form of tracheal support[31] with, for example, ceramic rings.[3]

Laryngeal oedema

Generalized myxoedema of hypothyroidism may involve the larynx, giving a characteristic hoarse voice. Laryngeal oedema has also been reported as an unusual presentation of thyroid lymphoma.[97] Laryngeal complications of tracheal intubation can be seen during the postoperative indirect laryngoscopy which is performed to identify recurrent laryngeal nerve damage. Oedema and traumatic lesions were noted in 4.6% of patients.[51]

While trauma to the larynx from the tracheal tube will cause minor swelling, laryngeal oedema is a rare cause of post-thyroidectomy respiratory obstruction. In the case reported by Bexton and Radford,[12] laryngeal oedema was associated with a large haematoma; it was postulated that the swelling was secondary to venous obstruction.

Hypocalcaemia

The incidence of hypocalcaemia will depend on the type of surgery performed. After thyroidectomy for large multinodular goitre, temporary hypocalcaemia requiring calcium replacement occurred in 20% of patients. This usually occurs about 36 h postoperatively. Only 3.1% of patients remained permanently hypocalcaemic.[30] Unintentional parathyroidectomy occurred in 11% of a series of 414 thyroidectomies. This might be reduced by more careful inspection of the thyroid capsule.[53]

Wound complications

Wound infection should be a rare complication and a well positioned incision should provide a good cosmetic result. Care should be taken during elevation of skin flaps to avoid damage to the anterior cutaneous nerve of the neck. Damage to this structure produces numbness, which could prove inconvenient, for example to men when shaving.[74]

Postoperative nausea and vomiting

Patients undergoing thyroidectomy are at a high risk for the development of postoperative nausea and vomiting (PONV)[84] and therefore are often used to study the anti-emetic properties of drugs. Granisetron,[29] lorazepam premedication,[52] propofol for maintenance of anaesthesia,[84] subhypnotic doses of propofol[24] and positive therapeutic suggestions during neurolept anaesthesia[20] have all been shown to be effective in reducing nausea and vomiting following thyroidectomy.

Postoperative pain

Patients usually tolerate thyroidectomy very well and require minimal postoperative analgesia. They often complain of a stiff neck because of the position during surgery, rather than pain from the site of the incision.

Future developments

There are various pressures upon clinicians to reduce bed occupancy. Thyroidectomy as an outpatient procedure has been described,[56] but patient selection, anaesthetic technique, careful observation before discharge, and community support are key factors in this situation. Interestingly, two of the 203 patients in this series required re-operation for postoperative bleeding.[56]

Minimally invasive techniques have been developed in many surgical subspecialties, including endocrine surgery. Laparoscopic adrenalectomy is widely practised and endoscopic parathyroidectomy has been reported.[65] What of the thyroid gland? Laser-induced reduction of thyroid tissue has been performed on an animal model,[93] but further work needs to be done before this can be used to treat hyperthyroid humans.

Summary

In summary, disease of the thyroid gland is common. Anaesthetists will be required to manage patients with hypothyroidism and hyperthyroidism and those requiring thyroidectomy. Since anaesthesia for thyroidectomy provides many challenges of airway management, the anaesthetist should pay particular attention to preoperative assessment of the airway and should be able to deal with acute airway complications in the perioperative phase

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References

1 Aadahl P, Nordgard S. Percutaneous dilatational tracheostomy in a patient with thyroid cancer and severe airway obstruction *Acta Anaesthesiol Scand* 1999; **43**: 483–5

2 Abdel Rahim AA, Ahmed ME, Hassan MA. Respiratory complications after thyroidectomy and the need for tracheostomy in patients with a large goitre. *Br J Surg* 1999; **86**: 88–90

3 Amedee RG, Mann WJ, Lyons GD. Tracheomalacia repair using ceramic rings. *Otolaryngol Head Neck Surg* 1992; **106**: 270–74

4 Anders HJ. Compression syndromes caused by substernal goitres. *Postgrad Med J* 1998; **74**: 327–9

5 Arts CH, Bax NM, Jansen M, Lips CJ, Vroom TM, van Vroonhoven TJ. Prophylactic total thyroidectomy in childhood for multiple endocrine neoplasia type 2A: preliminary results. *Ned Tijdschr Gen* 1999; **143**: 98–109

6 Asai T, Koga K, Vaughan RS. Respiratory complications associated with tracheal intubation and extubation. *Br J Anaesth* 1998; **80**: 767–75

7 Astwood EB. Treatment of hyperthyroidism with thiourea and thiouracil. *J Am Med Assoc* 1943; **122**: 78–81

8 Barker P, Mason RA, Thorpe MH. Computerised axial tomography of the trachea. A useful investigation when a retrosternal goitre causes symptomatic tracheal compression. *Anaesthesia* 1991; **46**: 195–8

9 Bennett MH, Wainwright AP Acute thyroid crisis on induction of anaesthesia. *Anaesthesia* 1989; **44**: 28–30

10 Bennett-Guerrero E, Kramer DC, Schwinn DA. Effect of chronic and acute thyroid hormone reduction on perioperative outcome. *Anesth Analges* 1997; **85**: 30–36

11 Belmont MJ, Wax MK, DeSouza FN. The difficult airway: cardiopulmonary bypass—the ultimate solution. *Head Neck* 1998; **20**· 266–9

12 Bexton MD, Radford R. An unusual case of respiratory obstruction after thyroidectomy. *Anaesthesia* 1982; **37**: 596

13 Black JW, Crowther AF, Shanks RG, Smith LH, Dornhurst AC. New adrenergic beta-receptor antagonist. *Lancet* 1964; **i**. 1080–81

14 Brain AIJ. The laryngeal mask—a new concept in airway management. *Br J Anaesth* 1983; **55**: 801–4

15 Charters P, Cave-Bigley D, Roysam CS. Should a laryngeal mask be routinely used in patients undergoing thyroid surgery? *Anesthesiology* 1991; **75**: 918–19

16 Christensen PA, Nissen LR. Treatment of thyroid storm in a child with dantrolene. *Br J Anaesth* 1987; **59**: 523

17 Clarke PM, Kozeis N. A complication of peribulbar block in a patient with exophthalmos. *Br J Anaesth* 1998; **81**: 615

18 Condon HA, Gilchrist E. Stanley Rowbotham. Twentieth century pioneer anaesthetist. *Anaesthesia* 1986; **41**: 46–52

19 Donati F, Plaud B, Meistelman C. A method to measure elicited contraction of laryngeal adductor muscles during anesthesia. *Anesthesiology* 1991; **74**: 827–32

20 Eberhart LH, Doring HJ, Holzrichter P, Roscher R, Seeling W. Theraputic suggestions given during neurolept anaesthesia decrease post-operative nausea and vomiting. *Eur J Anaesthesiol* 1998; **15**: 446–52

21 Eisele DW. Intraoperative electrophysiologic monitoring of the recurrent laryngeal nerve. *Laryngoscope* 1996; **106**: 443–9

22 Erskine RJ, Murphy PJ, Langton JA. Sensitivity of upper airway reflexes in cigarette smokers: effect of abstinence. *Br J Anaesthes* 1994, **73**: 298–302

23 Erskine RJ, Murphy PJ, Langton JA, Smith G. Effect of age on the sensitivity of upper airway reflexes. *Br J Anaesth* 1993; **70**: 574–5

24 Ewalenko P, Janny S, Dejonckheere M, Andry G, Wyns C. Antiemetic effect of subhypnotic doses of propofol after thyroidectomy. *Br J Anaesth* 1996; **77**: 463–7

25 Farling PA, Russell CFJ. Bilateral nodular goitre and ankylosing spondylitis (in press).

26 Fogarty D. Lingual thyroid and difficult intubation. *Anaesthesia* 1990; **45**: 251

27 Franklyn J. Thyrotoxicosis. *Prescrib J* 1999; **39**: 1–8

28 Freitas JE, Freitas AE. Thyroid and parathyroid imaging. *Semin Nucl Med* 1994; **24**: 234–45

29 Fujii Y, Saitoh Y, Tanaka H, Toyooka H. Prophylactic antiemetic therapy with granisetron in women undergoing thyroidectomy. *Br J Ancesth* 1998; **81**: 526–8

30 Gardiner KR, Russell CFJ. Thyroidectomy for large multinodular goitre. *J Roy Coll Surg Edin* 1995; **40**: 367–70

31 Geelhoed GW. Tracheomalacia from compressing goiter: management after thyroidectomy. *Surgery* 1988; **104**: 100–108

32 Gefke K, Andersen LW, Friesel E. Lidocaine given intravenously as a suppressant of cough and laryngospasm in connection with extubation after tonsillectomy. *Acta Anaesthesiol Scand* 1983; **27**: 111–12

33 Gittoes NJL, Miller MR, Daykin J, Sheppard MC, Franklyn JA. Upper airways obstruction in 153 consecutive patients presenting with thyroid enlargement. *Br Med J* 1996; **312**: 484

34 Greatorex RA, Denny NM. Application of the laryngeal mask airway to thyroid surgery and the preservation of the recurrent laryngeal nerve. *Ann R Coll Surg Engl* 1991; **73**: 352–4

35 Green WE, Shepperd HW, Stevenson HM, Wilson W. Tracheal collapse after thyroidectomy. *Br J Surg* 1979; **66**: 554–7

36 Hamilton WF, Forrest AL, Gunn A, Peden NR, Feely J. Beta-adrenoceptor blockade and anaesthesia for thyroidectomy. *Anaesthesia* 1984; **39**: 335–42

37 Harness JK, Fung L, Thompson NW, Burney RE, McLeod MK. Total thyroidectomy: complications and technique. *World J Surg* 1986; **10**: 781–6

38 Hobbiger HE, Allen JG, Greatorex RG, Denny NM. The laryngeal mask airway for thyroid and parathyroid surgery. *Anaesthesia* 1996; **51**: 972–4

39 Howells TH. Anaesthesia for goitre. *Anaesthesia* 1979; **34**: 85

40 Huang CJ, Hsu YW, Chen CC *et al*. Prevention of coughing induced by endotracheal tube during emergence from general anesthesia—a comparison between three different regimens of lidocaine filled in the endotracheal tube cuff. *Acta Anaesthesiol Sin* 1998; **36**: 81–6

41 Iwatake H, Iida J, Minami S, Sugano S, Hoshikawa T, Takeyama I. Transcutaneous intracordal silicon injection for unilateral vocal cord paralysis. *Acta Otolaryngol Suppl* 1996; **522**: 133–7

42 James ML. Endocrine disease and anaesthesia. *Anaesthesia* 1970; **25**: 232–52

43 Jori J, Rovo L, Czigner J. Vocal cord laterofixation as early treatment for acute bilateral abductor paralysis after thyroid surgery. *Eur Arch Otorhinolaryngol* 1998; **255**: 375–8

44 Kahaly GJ, Nieswandt J, Mohr-Kahaly S. Cardiac risks of hyperthyroidism in the elderly. *Thyroid* 1998; **8**: 1165–9

45 Kho HG, van Egmond J, Zhuang CF, Lin GF, Zhang GL. Acupuncture anaesthesia. Observations on its use for removal of thyroid adenomata and influence on recovery and morbidity in a Chinese hospital. *Anaesthesia* 1990; **45**: 480–85

46 Klein SM, Greengrass RA, Knudsen N, Leight G, Warner DS. Regional anesthesia for thyroidectomy in two patients with amiodarone-induced hyperthyroidism. *Anesth Analges* 1997; **85**: 222–4

47 Knighton JD, Crosse MM. Anaesthetic management of childhood thyrotoxicosis and the use of esmolol. *Anaesthesia* 1997; **52**: 67–70

48 Kocak S, Aydintug S, Ozbas S, Kocak I, Kucuk B, Baskan S. Evaluation of vocal cord function after thyroid surgery. *Eur J Surg* 1999; **165**: 183–6

49 Konrad C, Gerber H, Schnider T, Schupfer G. Is an alkalinized lignocaine solution a better topical anaesthetic for intratracheal application? *Eur J Anaesthesiol* 1997, **14**: 616–22

50 Kulkarni RS, Braverman LE, Patwardhan NA. Bilateral cervical plexus block for thyroidectomy and parathyroidectomy in healthy and high risk patients. *J Endocrinol Invest* 1996; **19**: 714–18

51 Lacoste L, Gineste D, Karayan J *et al.* Airway complications in thyroid surgery. *Ann Otol Rhinol Laryngol* 1993; **102**: 441–6

52 Laraki M, el Mouknia M, Bouaguad A, Idali B, Benaguida M. Prevention of postoperative nausea and vomiting by lorazepam. *Cahiers d'Anesthesiol* 1996; **44**: 159–62

53 Lee NJ, Blakey JD, Bhuta S, Calcaterra TC. Unintentional parathyroidectomy during thyroidectomy. *Laryngoscope* 1999; **109**: 1238–40

54 Levelle JP, Jopling MW, Sklar GS. Perioperative hypothyroidism: an unusual postanesthetic diagnosis *Anesthesiology* 1985, **63**: 195–7

55 Lind P, Langsteger W, Molnar M, Gallowitsch HJ, Mikosch P, Gomez I. Epidemiology of thyroid diseases in iodine sufficiency. *Thyroid* 1998; **8**: 1179–83

56 Lo Gerfo P. Local/regional anesthesia for thyroidectomy evaluation as an outpatient procedure. *Surgery* 1998; **124** 975–8

57 MacIntyre PA, Ansari KA. Sevoflurane for predicted difficult tracheal intubation. *Eur J Anaesthesiol* 1998; **15**: 462–6

58 Mangold JH, Morgan AK, Earle DJ, Young AE, Croft DN. Lugol's iodine: its effect on thyroid blood flow in patients with thyrotoxicosis. *Br J Surg* 1985; **72**: 45–7

59 Maroof M, Siddique M, Khan RM. Post-thyroidectomy vocal cord examination by fibreoscopy aided by the laryngeal mask airway. *Anaesthesia* 1992; **47**: 445

60 Mathes DD. Treatment of myxedema coma for emergency surgery. *Anesth Analges* 1998; **6**: 450–51

61 McCoy ÉP, Mirakhur RK. The Levering laryngoscope *Anaesthesia* 1993; **48** 516–19

62 McHenry CR, Piotrowski JJ. Thyroidectomy in patients with marked thyroid enlargement airway management, morbidity, and outcome. *Am Surg* 1994, **60** 5865–91

63 Mendel P, Fredman B, White PF. Alfentanil suppresses coughing and agitation during emergence from isoflurane anaesthesia. *J Clin Anesth* 1995; **7**: 114–18

64 Meurisse M, Faymonville ME, Joris J, Nguyen Dang D, Defechereux T, Hamoir E. Endocrine surgery by hypnosis From fiction to daily clinical application. *Ann d'Endocrinol* 1996; **57**: 494–501

65 Miccoli P, Bendinelli C, Vignali E *et al.* Endoscopic parathyroidectomy report of initial experience. *Surgery* 1998; **124**: 1077–80

66 Mostbeck A, Galvan G, Bauer P *et al.* The incidence of hyperthyroidism in Austria from 1987 to 1995 before and after an increase in salt iodization in 1990. *Eur J Nucl Med* 1998; **25**: 367–74

67 Murkin JM. Anesthesia and hypothyroidism A review of thyroxine physiology, pharmacology and anesthetic implications. *Anesth Analges* 1982; **61**: 371–83

68 Naito Y, Sone T, Kataoka K, Sawada M, Yamazaki K. Thyroid storm due to functioning metastatic thyroid carcinoma in a burn patient. *Anesthesiology* 1997; **87**: 433–5

69 Nandwani N, Raphael JH, Langton JA. Effect of an upper respiratory tract infection on upper airway reactivity *Br J Anaesth* 1997; **78**: 352–5

70 Nemiroff PM, Katz AD. Extralaryngeal divisions of the recurrent laryngeal nerve: surgical and clinical significance. *Am J Surg* 1982, **144**: 466–9

71 Netterville JL, Coleman SC, Smith JC, Smith MM, Day TA, Burkey BB. Management of substernal goiter. *Laryngoscope* 1998, **108** 1611–17

72 Nimmo WS, Rowbotham DJ, Smith G. eds. *Anaesthesia*, 2nd edn. Oxford Blackwell, 1994. 1107

73 Pugh S, Lalwani K, Awal A. Thyroid storm as a cause of loss of consciousness following anaesthesia for emergency caesarean section *Anaesthesia* 1994; **49**. 35–7

74 Ready AR, Barnes AD. Complications of thyroidectomy. *Br J Surg* 1994; **81**. 1555–6

75 Rose DK, Cohen MM The airway problems and predictions in 18500 patients. *Can J Anaesth* 1994; **41**. 372–83

76 Rowbotham E *Anaesthesia for Operations for Goitre*. Oxford. Blackwell, 1945

77 Rowe-Jones JM, Rosswick RP, Leighton SE. Benign thyroid disease and vocal cord palsy. *Ann Roy Coll Surg Engl* 1993, **75**: 241–4

78 Santos GH, Ghalili K. Axillosubclavian vein thrombosis produced by retrosternal thyroid. *Chest* 1990, **98**: 1281–3

79 Shaha A, Alfonso A, Jaffe BM Acute airway distress due to thyroid pathology. *Surgery* 1987, **102** 1068–74

80 Singh H, Rao YN, Prassanna A. Anaesthesia for huge goitre. *Anaesthesia* 1978; **33**: 555–6

81 Singh SD, Williams AJ. The prevalence and incidence of medical conditions in healthy pharmaceutical company employees who volunteer to participate in medical research. *Br J Clin Pharmacol* 1999; **48**: 25–31

82 Singh V, Catlett JP. Hematologic manifestations of thyroid disease. *Endocrinologist* 1998; **8**: 87–91

83 Sinha PK, Dubey PK, Singh S. Identifying tracheomalacia *Br J Anaesth* 2000; **84**: 127–8

84 Sonner JM, Hynson JM, Clark O, Katz JA Nausea and vomiting following thyroid and parathyroid surgery. *J Clin Anesth* 1997, **9**: 398–402

85 Strube PJ. Thyroid storm during beta blockade. *Anaesthesia* 1984, **39** 343–6

86 Stehling LC. Anesthetic management of the patient with hyperthyroidism. *Anesthesiology* 1974; **41** 585–95

87 Swadia VN, Swadia ND, Sabnis SS. Problems in anaesthesia for huge thyroid goitres. *Br J Anaesth* 1981; **53** 963–5

88 Tanigawa K, Yoshitaka I, Sadayuki I. Protection of the recurrent laryngeal nerve during neck surgery. *Anesthesiology* 1991; **74**: 966–7

89 Thompson NW, Nishiyama RH, Harness JK. Thyroid carcinoma: current controversies *Curr Probl Surg* 1978; **15** 1–67

90 Todesco J, Williams RT Anaesthetic management of a patient with a large neck mass *Can J Anaesth* 1994, **41** 157–60

91 Tsubokawa T, Yamamoto K, Kobayashi T. Propofol clearance and distribution volume increase in patients with hyperthyroidism. *Anesth Analges* 1998; **87**. 195–9

92 Van Heurn LW, Schaap C, Sie G *et al* Predictive DNA testing for multiple endocrine neoplasia 2: a therapeutic challenge of prophylactic thyroidectomy in very young children. *J Pediatr Surg* 1999; **34** 568–71

93 Van Sanden H, Hauptmann G. Laser application for minimal invasive reduction of thyroid gland tissue. *Eur J Med Res* 1997; **2** 527–34

94 Vellar ID. Thomas Peel Dunhill: pioneer thyroid surgeon *Austral New Zeal J Surg* 1999; **69**: 375–87

95 Vijayakumar HR, Thomas WO, Ferrara JJ. Peri-operative management of severe thyrotoxicosis with esmolol. *Anaesthesia* 1989; **44**: 406–8

96 Wakeling HG, Ody A, Ball A. Large goitre causing difficult intubation and failure to intubate using the intubating laryngeal mask airway: lessons for next time. *Br J Anaesth* 1998; **81**: 979–81

97 Watson C. Laryngeal oedema complicating thyroid lymphoma. *J Laryngol Otol* 1988; **102**: 947–50

98 Watters MP, McKenzie JM. Inhalational induction with sevoflurane in an adult with severe complex central airways obstruction. *Anaesth Intensive Care* 1997; **25**: 704–6

99 Welbourn RB. *The History of Endocrine Surgery.* New York: Praeger, 1990: 19–82

100 Whitlock RI. Headrest for oral surgery. *Br J Oral Surg* 1964; **2**: 104

101 Zatterale A, Stabile M, Nunziata V, Di Giovanni G, Vecchione R, Ventruto V. Multiple endocrine neoplasia type 2 (Sipple's syndrome): clinical and cytogenetic analysis of a kindred. *J Med Genet* 1984; **21**: 108–11

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Parathyroid disease and calcium metabolism

R. Mihai and J. R. Farndon

Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

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Historical notes

The parathyroid glands were first described in 1850 at the autopsy of an Indian rhinoceros by Sir Richard Owen, conservator of the Hunterian Museum of the Royal College of Surgeons of England.[69] Thirty years later, an illustrated anatomical and histological description in animals and humans was given by Ivar Sandstrom, a medical student from Uppsala.[82] Felix Mandl in Vienna was the first to undertake parathyroid surgery in 1925, successfully removing a parathyroid adenoma in a patient with osteitis fibrosa cystica.[58] In the same period, the first American patient diagnosed with hyperparathyroidism needed seven operations before an adenoma was found in the mediastinum.[6]

Parathyroid hormone (PTH) extracts were first prepared in the early 1920s.[17 38] The understanding of parathyroid physiology was influenced by the landmark metabolic studies of Fuller Albright in the Renal Stone Clinic or 'Quarry' at the Massachusetts General Hospital.[1] In the 1980s, PTH was sequenced, its gene[42 99] and its receptor were cloned[84] and improved chemiluminescent immunoassays for intact PTH were developed. The recent cloning of the calcium receptor in 1993[11] opened new perspectives for understanding the regulation of parathyroid function.

Parathyroid embryology and anatomy

In all vertebrate species, the parathyroid glands are derived from the endoderm of the pharyngeal pouches.[35] Before the appearance of the thymic rudiment from the third pharyngeal pouch, its epithelium differentiates as the primordium of the inferior parathyroid gland. Parathyroid III rudiments remain connected to the thymus and are carried with it in its caudal migration. They are usually found close to the inferior thyroid poles but may descend with the thymus into the thorax or may not descend at all, remaining above the carotid bifurcation.

The superior parathyroid glands develop from the fourth pharyngeal pouches and are therefore referred to as 'parathyroid IV'. They come into relation with the lateral lobes of the thyroid gland to which they become anchored and, therefore, usually remain cranial to parathyroid III. The superior parathyroid glands are more constant in location and are usually midway along the posterior thyroid borders (where the inferior thyroid artery enters the gland or at its intersection with the recurrent laryngeal nerve).

Gilmour, after dissection of 547 cadavers, found four parathyroid glands in the majority (87%); the others had three glands (6%), two glands (0.1%) or supernumerary glands.[32]

'Classical' embryology cannot explain the involvement of the parathyroid glands in multiple endocrine neoplasia type 2 (see review by Holdsworth in this issue), where patients present with tumours of endocrine cells of neuroectodermal origin, i.e. medullary thyroid carcinomas (thyroid parafollicular C cells) and phaeochromocytomas (adrenal medulla). It has been postulated that the parathyroid glands initially contain both endodermal and ectodermal elements and that, presumably, the endodermal component predominates when the functional stage of hormone production begins.[73] Although not agreed by all,[61] the mesenchymal components of the parathyroids are considered to have ectodermal origin, similar to that from the glands arising from the pharyngeal and buccal epithelium (e.g. pituitary, thyroid, salivary).[16] Furthermore, morphological characteristics of the parathyroid glands support an ectodermal origin: immunohistochemically, normal and neoplastic human parathyroid cells exhibit neuroendocrine markers, such as neurone-specific enolase, chromogranin and dopa decarboxylase and rat parathyroid cells contain the neuroendocrine marker, protein S100.[103] Taken together with prior findings of somatostatin, gastrin and pancreatic polypeptide in human parathyroid glands,[100] it is postulated that parathyroid glands and tumours contain neural crest elements.

Overview of calcium homeostasis

Calcium is an essential element throughout the phylogenetic tree, in mammals it has important extracellular and intracellular functions (Table 1). In humans, there are about 27 000 mmol of calcium in bone contained in hydroxyapatite and only 70 mmol of calcium within intracellular and extracellular fluids. The extracellular

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Table 1 Site and function of calcium in humans (adapted from 12)

Form	Locations	Mass (% of total)	Functions
Intracellular soluble	Cytosol, nucleus, endoplasmic reticulum, mitochondria	0.2 mg	Intracellular second messenger, action potentials, nerve conduction, contraction, motility, metabolic regulation, cytoskeletal function, cell division, secretion
Intracellular insoluble (sequestered)	Cytosol, nucleus, endoplasmic reticulum, mitochondria	9 g (0.9)	Structural integrity, storage
Extracellular soluble	Extracellular fluids	1 g (0.1)	Blood clotting, exocytosis, contraction. intercellular adhesion
Extracellular insoluble	Bones, teeth	~1 kg (99)	Protection, locomotion, mineral storage

calcium occurs in three forms: as non-ionized, protein-bound (approximately 50%), as calcium–anion complexes (5%) and as ionized divalent cations (approximately 45%). For this reason the albumin concentration affects the amount of total calcium and the corrected concentration is always reported (reference range 2.20–2.70 mmol litre^{-1}). It is the free (ionized) extracellular calcium concentration ($[Ca^{2+}]_{ext}$) that influences all the physiological effects.

$[Ca^{2+}]_{ext}$ is maintained within a narrow range (1.0–1.3 mM) by regulating the fluxes of Ca^{2+} into and out of the skeleton and across the epithelial cells of the kidneys and intestine. This tight control of $[Ca^{2+}]_{ext}$ is achieved despite significant fluxes of Ca^{2+} across the Ca^{2+}-regulating tissues. For example, 10 g of Ca^{2+} is filtered daily (and potentially lost) by the kidney, but 9.8 g is reabsorbed.

Two major components of the control of calcium metabolism have been defined. First, Ca^{2+} sensors on cells recognize and respond to small, physiologically meaningful changes in the $[Ca^{2+}]_{ext}$, leading to appropriate changes in cellular function. For example, in response to hypercalcaemia, parathyroid cells secrete less PTH and C cells of the thyroid secrete more calcitonin. Second, effector tissues (intestine, kidney and bone) respond to calciotropic hormones with changes in the transport of ions, to restore $[Ca^{2+}]_{ext}$ to normal.

Calcium homeostasis is controlled by vitamin D and the hormones PTH and calcitonin.

Parathyroid hormone

PTH plays a central role in the rapid control of calcium homeostasis. Its co-ordinated actions on bone, kidney and intestine increase the flow of calcium into the extracellular fluid and increase the concentration of calcium in blood. PTH is an 84 amino acid peptide with a molecular weight of 9500 Da and a short half-life (2–3 min) in the circulation before being cleaved into an amino-terminal fragment (amino acids 1–34) and a carboxy-terminal fragment. Only the 1–34 fragment retains biological activity. PTH binds to specific receptors on the membrane of target cells: renal and bone cells, fibroblasts, chondrocytes, vascular smooth muscle, adipocytes and placental trophoblasts.[12]

Effects of PTH on the kidney

The distribution of PTH receptors and that of Ca^{2+} receptors overlap in the distal nephron,[76] allowing $[Ca^{2+}]_{ext}$ to have a direct effect (through action on Ca^{2+} receptors) and an indirect influence (through modulation of plasma PTH concentrations) on the renal component of calcium homeostasis. The intracellular mediator for PTH effects is intracellular cyclic adenosine monophosphate (cAMP), whose urinary secretion is a biochemical marker of PTH activity. The effects of PTH on the kidney include:

(i) Increased extraction of Ca^{2+} from the glomerular filtrate. The major physiological effect of PTH is enhancement of Ca^{2+} reabsorption. This is due to effects on: the thick ascending loop of Henle (it increases the transepithelial voltage gradient that drives passive Ca^{2+} transport); the granular portion of the distal convoluted tubule (it induces translocation of preformed Ca^{2+} channels on the cell surface to enhance luminal Ca^{2+} entry); and the collecting tubules (it enhances the activity of Na^+/Ca^{2+} exchangers). Despite its direct effect of increasing Ca^{2+} reabsorption, excessive PTH secretion increases urinary Ca^{2+} excretion because of the high load of filtered Ca^{2+} resulting from hypercalcaemia. At any given Ca^{2+} load, Ca^{2+} clearance is decreased by PTH and increased in the absence of PTH.

(ii) Increased phosphate excretion. PTH acts on the proximal and distal convoluted tubules and inhibits Na^+-dependent phosphate transport.

(iii) Increased bicarbonate clearance and alkalinization of the urine result from inhibition of bicarbonate reabsorption in the proximal renal tubule. In patients with primary hyperparathyroidism, excessive secretion of PTH leads to a type of renal tubular acidosis.

(iv) Increased free water clearance and increased urinary flow. Inhibition of Na^+ reabsorption in the proximal tubule leads to an increase in Na^+ loading of the distal tubule. At this point, Na^+ is reabsorbed proportionally more than the associated water, leading to an increase in free water clearance.

(v) Increased activity of vitamin D1α hydroxylase.

(vi) In primary hyperparathyroidism, the renal effects of PTH are observed as hypercalciuria, hypophosphataemia, hyperchloraemic acidosis, polyuria, polydypsia and an increased excretion of nephrogenous fraction of cAMP.

Effects of PTH on the bone

PTH produces both anabolic and catabolic effects which can be distinguished as early phase (mobilization of Ca^{2+} from bone in rapid equilibrium with the extracellular fluids) and late phase (increased synthesis of bone enzymes, such as lysosomal enzymes which promote reabsorption and bone remodelling).

Osteoblasts are probably the primary bone cells that interact directly with PTH while osteoclasts seem to be devoid of PTH receptors. PTH inhibits osteoblasts and stimulates osteoclast-mediated bone resorption, leading to an increase in alkaline phosphatase and increased urinary hydroxyproline (markers of increased breakdown of bone matrix). In primary hyperparathyroidism, changes in alkaline phosphatase and hydroxyproline are markers of bone disease.

Effects of PTH on the intestine

PTH does not directly affect gastrointestinal absorption of Ca^{2+}. Its effects are mediated indirectly through regulation of synthesis of $1,25(OH)_2D_3$ in the kidney.

Other effects

Studies *in vitro* have identified effects whose physiological significance is not yet understood, including changes in blood flow in the coeliac axis, enhanced lipolysis in adipocytes and increased gluconeogenesis in liver and kidney.

Calcitonin

Calcitonin is a 32 amino acid protein secreted by the parafollicular C cells of the thyroid in response to high $[Ca^{2+}]_{ext}$. It induces a decrease in serum calcium by inhibiting osteoclast activity and by increasing urinary excretion of Ca^{2+}. Its exact physiological role in humans is uncertain since it has few long-term effects on serum calcium. Its complete absence following total thyroidectomy needs no replacement and severe excess of calcitonin (such as in patients with medullary thyroid carcinomas) has no major effect on calcium metabolism.

Control of parathyroid hormone secretion

Extracellular calcium

$[Ca^{2+}]_{ext}$ is the major determinant of the rate of PTH secretion: slight reductions in $[Ca^{2+}]_{ext}$ increase promptly the rate of PTH secretion. The magnitude and duration of hypocalcaemic stress has a significant effect on the manner in which the homeostatic system responds. The initial changes in rate of PTH secretion in response to low $[Ca^{2+}]_{ext}$ take place within seconds because of the release of preformed hormones from storage granules. Within 15–30 min, there is also an increase in the net rate of PTH synthesis. If the hypocalcaemic stimulus persists, modest increases in the amount of PTH mRNA take place (in 3–12 h in rats *in vivo* or within 1–2 days in bovine parathyroid cells *in vitro*). Prolonged hypocalcaemia promotes parathyroid cellular hypertrophy and proliferation within days to weeks (data reviewed in reference 74). The inverse sigmoidal relationship between PTH secretion and $[Ca^{2+}]_{ext}$ has been documented *in vivo* and *in vitro* and can be described using a four-parameter model.[9] In addition to its effect on PTH secretion, $[Ca^{2+}]_{ext}$ modulates the synthesis of PTH and the intracellular degradation of PTH into smaller fragments.

In 1991, Brown thought that a body of indirect evidence suggested that $[Ca^{2+}]_{ext}$ acted on parathyroid cells through a cell surface, receptor-like mechanism.[10] A plasma membrane Ca^{2+} receptor was subsequently cloned from bovine parathyroid cells[11] and its presence demonstrated on human cells from parathyroid adenomas.[30] This was the first example of a cell surface receptor recognizing an ion rather than a molecule as a principal ligand. The current knowledge about Ca^{2+} receptor intracellular signalling is summarized in Fig. 1.

The human Ca^{2+} receptor is encoded by a gene on chromosome 3q13-21 and consists of 1078 amino acids. The predicted Ca^{2+} receptor protein has a large extracellular amino-terminus (which binds polycationic Ca^{2+} receptor agonists), a central core with seven membrane-spanning helices (documenting that the Ca^{2+} receptor is a G-protein-coupled receptor) and an approximately 200 amino acid carboxy-terminal intracytoplasmic tail.[11 12] Over 30 different mis-sense mutations have been identified in kindreds with familial hypocalciuric hypercalcaemia.[72] Mutations that activate the Ca^{2+} receptor have also been identified and lead to familial hypoparathyroidism. A knock-out mouse model of inherited human Ca^{2+} receptor gene defects has been reported: heterozygous animals (i.e. Ca^{2+} receptor$^{+/-}$) reproduce most features of familial hypocalciuric hypercalcaemia and homozygous mutant mice (i.e. Ca^{2+} receptor$^{-/-}$) display markedly elevated $[Ca^{2+}]_{ext}$, increased PTH concentrations and parathyroid gland hyperplasia, as do patients with severe neonatal hyperparathyroidism.[45]

The Ca^{2+} receptor is widely expressed, both on cells involved with control of $[Ca^{2+}]_{ext}$ (e.g. parathyroid, calcitonin-secreting and bone cells) and also on cells not involved in Ca^{2+} homeostasis (e.g. pituitary, placenta, keratinocytes and gastrin-secreting cells).

A different membrane Ca^{2+}-sensor has been identified on parathyroid, proximal tubule and human placenta using immunocytochemistry.[49] This approximately 500 kDa protein is a member of the low density lipoprotein receptor

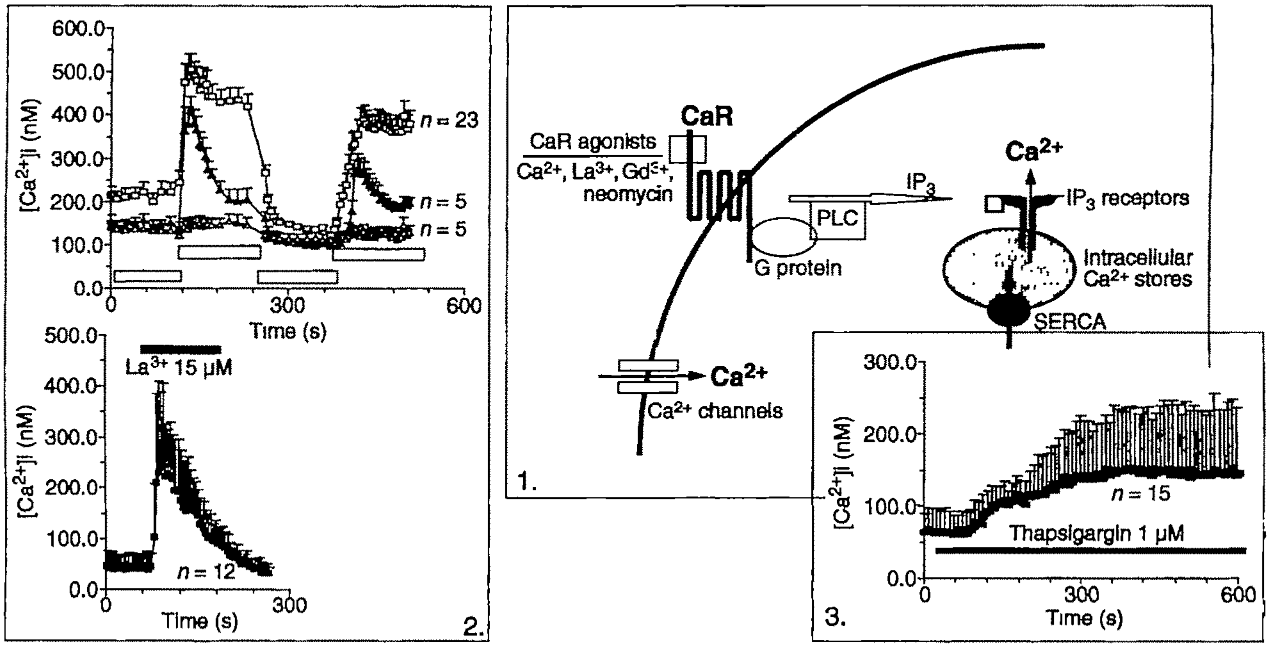

Fig 1 (1) Schematic representation of the Ca^{2+} receptor's signalling mechanisms Ca^{2+} receptor agonists bind to the extracellular domain of the Ca^{2+} receptor and trigger activation of the G protein–phospholipase C (PLC) pathway. PLC generates inositol-trisphosphate (IP_3), which binds to specific receptors situated on intracellular Ca^{2+} stores Upon binding of IP_3 the three-dimensional structure of IP_3 receptors changes and allows the release of Ca^{2+}. The responsiveness of IP_3 receptors modulates the amplitude of $[Ca^{2+}]_i$ responses following activation of the Ca^{2+} receptor.[63] The filling state of the intracellular Ca^{2+} stores is maintained by the action of specific Ca^{2+} pumps, i e the smooth endoplasmic reticulum Ca^{2+}-ATPases (SERCA) (2) The graphs illustrate changes in cytoplasmic concentration of calcium ($[Ca^{2+}]_i$) in parathyroid cells. $[Ca^{2+}]_i$ was measured using quantitative fluorescent microscopy in Fura-2-loaded cells. The upper panel illustrates responses to changes in $[Ca^{2+}]_{ext}$ from 0.5 to 3 mM. The lower panel illustrates $[Ca^{2+}]_i$ responses to the Ca^{2+} receptor agonist lanthanum (La^{3+}, 15 μM). (3) $[Ca^{2+}]_i$ increases rapidly following incubation with thapsigargin, an inhibitor of SERCA.

superfamily[59] and has recently been cloned.[44] Its role in controlling $[Ca^{2+}]_i$ and PTH secretion requires further study.

Magnesium

In acute studies *in vivo* and *in vitro*, changes in the extracellular concentration of magnesium ($[Mg^{2+}]_{ext}$) have similar effects to changes in $[Ca^{2+}]_{ext}$. As Mg^{2+} is a much less potent Ca^{2+} receptor agonist[11] and because the blood concentration is lower than that of Ca^{2+}, changes of $[Mg^{2+}]_{ext}$ in the physiological range have little influence on PTH secretion.

High $[Mg^{2+}]_{ext}$ (as in renal failure) can inhibit PTH secretion. Chronic severe hypomagnesaemia causes a paradoxical decrease in PTH secretion rather than the expected increase, suggesting that intracellular Mg^{2+} deficiency interferes with secretory mechanisms and blocks PTH secretion.[2]

Vitamin D

The main effect of vitamin D is a specific, dose-dependent and reversible suppression of PTH gene transcription.[80] Furthermore, 1,25-$(OH)_2D_3$ suppresses the secretory process at low $[Ca^{2+}]_{ext}$ and increases the intracellular degradation of PTH.

Catecholamines

The responsiveness of normal parathyroid tissue to β-adrenergic agonists is well established, but the role of catecholamines in the pathophysiology of the glands is undefined.

Specific α-adrenergic agonists inhibit PTH secretion *in vitro* but have little effect *in vivo*. Epinephrine increases PTH secretion by acting on β-adrenergic receptors. The response is transient and is influenced by $[Ca^{2+}]_{ext}$: minimal effects occur during hypercalcaemia whereas the response becomes more dramatic as the $[Ca^{2+}]_{ext}$ is lowered. β-Adrenergic antagonists (propranolol) reduce PTH concentrations acutely in normal subjects. Propranolol neither modulates basal output nor inhibits isoproterenol-induced secretion from forearm autografts of hyperplastic parathyroid tissue, suggesting an altered responsiveness to β-adrenergic agents in patients with secondary hyperparathyroidism.[25] Dopamine stimulates secretion from bovine parathyroid glands *in vitro* and *in vivo* by releasing a storage pool of intact PTH, but no effect has been documented in humans.

Steroids

Glucocorticoids stimulate PTH release *in vitro* in a dose-dependent manner.[89] Oestrogen and progesterone stimulate

PTH secretion from bovine parathyroid cells. Furthermore, oestrogen may modulate the sensitivity of PTH secretion to regulation by $[Ca^{2+}]_{ext}$,[8] directly stimulate PTH gene transcription and secretion and reduce peripheral actions of PTH.[48]

Ultradian rhythms of PTH secretion

Narrow pulses (half-life <60 s) and bursts of narrow pulses of PTH secretion can be detected, but the time-keeping mechanism has not been identified. The pulsatile component of PTH secretion accounts for 25% of total release.[81] During induced hypocalcaemia, a brisk increase in plasma PTH appears in the first 30 min, with a preferential increase in the pulsatile component of secretion (>10-fold) through increased frequency and amplitude of secretory bursts. The tonic secretion increases only during steady-state hypocalcaemia. Secretory bursts disappear during the initial 30 min of induced hypercalcaemia and reappear in the subsequent 75 min with a decreased frequency and amplitude.[83]

Primary hyperparathyroidism

Epidemiology

Primary hyperparathyroidism is a common endocrine disorder, with an incidence influenced by the means of diagnosis and the population studied. The increased use of multichannel biochemical analysers has influenced the pattern of presentation. In the UK the incidence was estimated to be about 25 per 100 000 general population, the majority of subjects being asymptomatic.

Aetiology

Most patients have a single parathyroid adenoma (80%); multiple gland hyperplasia is found in 10–20% of patients and parathyroid carcinoma is rare (1%). Monoclonality occurs in parathyroid adenomas[3 29] and can be found in sporadic multigland hyperplasia[23] and familial multiple endocrine neoplasia (MEN) type 1.[28 91] At least three tumour-specific molecular genetic defects are implicated in the development of parathyroid tumours:

Cyclin D1

Some parathyroid adenomas present a clonal chromosomal inversion by which the 5′-regulatory region of the PTH gene (normally located at chromosomal position 11p15) is juxtaposed to the PRAD1/cyclin D_1 oncogene located at 11q13.[65 78] This rearrangement leads to overexpression of the cyclin D_1 oncogene, a cell cycle regulator overexpressed in many types of cancer.[5]

Loss of a tumour suppressor gene

This has been suggested by the loss of heterozygosity in >25% of parathyroid adenomas on chromosome arms 1p, 6q, 11p, 11q and 15q.[90] None of these tumour suppressor genes has yet been identified and cloned. The tumour suppressor gene p53 shows no mutations in parathyroid adenomas or carcinomas[36] and allelic loss of the p53 gene has been identified in only a minority of carcinomas.[18]

Retinoblastoma gene deletion

This occurs commonly in parathyroid carcinomas and has potential diagnostic, prognostic and therapeutic implications.[19]

As many as 15–20% of patients with primary hyperparathyroidism gave a history of previous irradiation but an aetiological relationship cannot be established in individual cases. Analysis of a cohort (2555 patients, follow up 36 years) identified a dose–response relationship, with an excess relative risk increased significantly by 0.11/centigray and not influenced by gender or age at first presentation.[85]

Mechanisms for functional abnormalities in primary hyperparathyroidism

Different mutations identified in parathyroid adenomas may explain the abnormal growth or proliferation of parathyroid cells but do not account for the disordered function in primary hyperparathyroidism. PTH secretion in primary hyperparathyroidism is not influenced by changes in calcium within the physiological range because of a decreased sensitivity to $[Ca^{2+}]_{ext}$, which results in a shift to the left of the sigmoidal relationship and therefore a higher set-point. A specific abnormality of the mechanism(s) controlling secretion in individual adenomatous cells is suggested by the general lack of correlation between the size of the tumour and the severity of biochemical abnormalities (i.e. PTH concentration and hypercalcaemia) (Fig. 2). Overall, the excessive PTH secretion is the result of increased basal secretion and increased frequency and amplitude of PTH pulses.[39]

A tempting hypothesis is that, in sporadic parathyroid tumours, there are defects in the gene encoding the recently cloned Ca^{2+} receptor.[11] However, no such mutations have been identified in such patients[46] and allelic loss appeared in <10% of tumours.[93] The role of mutations in the Ca^{2+} receptor gene in the pathogenesis of primary hyperparathyroidism, therefore, remains controversial.

The role of vitamin D in the pathogenesis of primary hyperparathyroidism has been investigated extensively. Preoperative serum calcitriol concentrations correlate inversely with calcitriol receptor number in normal parathyroid tissue but not in parathyroid adenomas.[97] Vitamin D receptor (VDR) gene polymorphism could also be important: 60% of postmenopausal women with primary hyperparathyroidism express the VDR genotype *bb*, compared with 33.3% in controls. As the *b* allele has been linked to decreased transcriptional activity or messenger RNA stability, the *bb* genotype will reduce VDR expression, which may impede regulatory actions of vitamin D and contribute to parathyroid tumorigenesis.[13]

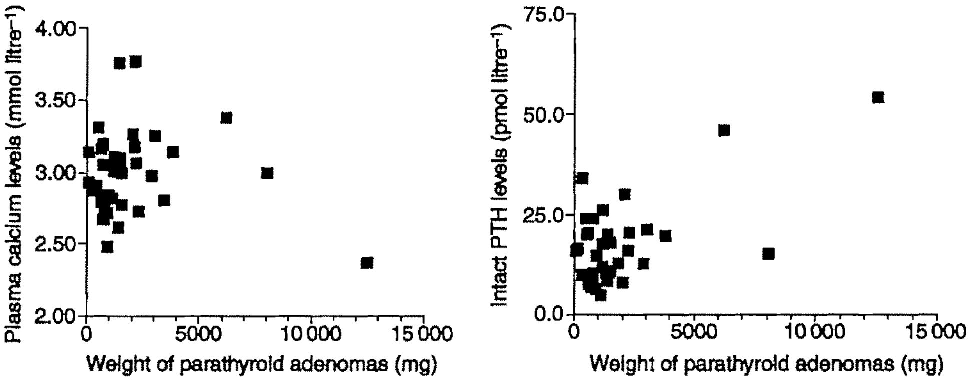

Fig 2 Lack of correlation between the weight of parathyroid adenomas and the biochemical abnormalities. In 37 patients with primary hyperparathyroidism, the weight of parathyroid adenomas was determined immediately after surgical removal. Preoperative values for calcium (corrected for albumin concentration) and PTH were recorded Intact PTH (1–84) was measured using a chemiluminescent assay (Immulite, DPC, Gwynedd, UK; coefficient of variance 4 7% and 5.5% for intrassay and interassay precision, respectively).

Clinical picture of primary hyperparathyroidism

The classical picture of 'moans, groans and stones' is rarely seen today. Instead, many non-specific symptoms may be elicited on direct questioning. The assessment and assignment of these symptoms provide a major problem, especially in the elderly.

Asymptomatic HPT

Currently most patients present with no or minimal symptoms. When no treatment is offered to these patients, follow-up for 10 yr reveals that most deteriorate (in one study, 26% developed a need for surgery and 24% died[86]). The arguments for offering surgical treatment to asymptomatic patients are presented later.

Renal manifestations

Renal involvement used to occur in 60–70% of patients but early diagnosis has reduced the incidence to 10–20% and many patients now lack renal manifestations despite having had the disease for many years.

Anatomical (nephrolithiasis and nephrocalcinosis) and functional (a spectrum of tubular and glomerular disorders) abnormalities occur. In severe primary hyperparathyroidism, impairment of proximal tubular function causes proximal tubular acidosis type II, aminoaciduria, glycosuria and nephrogenous diabetes insipidus. Functional changes can occur in the absence of any radiographic demonstrable renal calcification.

The pathogenesis of nephrolithiasis remains unclear since hypercalciuria does not correlate directly with stone formation. The propensity for crystallization and crystal growth of stone-forming constituents of urine is increased by urinary acidosis (i.e. PTH effects on bicarbonate transport in the proximal tubule).

Skeletal involvement

The incidence of osteitis fibrosa cystica has decreased sharply from >50% in the 1930s to the 1950s to 9% in the 1970s and to nearly zero in patients diagnosed by screening. Furthermore, patients with mild disease have already experienced major bone loss at diagnosis and, although parathyroidectomy has an initial positive effect on bone mineralization, there is no long-term advantage.[21] Increased bone resorption is associated with enhanced bone formation. There are region-specific differences in bone mass: it is low in areas with cortical bone (such as the radius) and normal or high in vertebrae and iliac crest (trabecular bone). Pathological fractures and brown tumours are now rare.

Articular manifestations

Chondrocalcinosis, pseudogout, juxta-articular erosions, traumatic synovitis, periarthritis and pericapsular calcification can occur.

Neuromuscular and neuropsychiatric manifestations

The real incidence of these symptoms is difficult to evaluate because some are so non-specific. Extreme weakness and fatigue, particularly involving proximal musculature of the lower extremities, can be present and improves postoperatively. Depression, personality changes, memory impairment and, occasionally, overt psychosis can occur. Obtunded consciousness occurs only when the serum calcium is extremely elevated.

Gastrointestinal involvement

Peptic ulcer can be a true manifestation of primary hyperparathyroidism and in a minority of patients, ulcers are part of Zollinger–Ellison syndrome or MEN1 with gastrin-producing tumours. However, it is not worth screening for MEN1 syndromes in patients with apparently sporadic primary hyperparathyroidism.[24]

Pancreatitis may also occur but a cause–effect relationship is uncertain. In acute primary hyperparathyroidism, 25% of patients may have pancreatitis. Normocalcaemia in a patient with severe acute pancreatitis should raise the question of primary hyperparathyroidism as an aetiological factor since pancreatic saponification and calcium binding can produce a spuriously low serum calcium concentration.

Table 2 General symptoms found in patients with primary hyperparathyroidism

System affected	Symptoms
Renal	Polyuria, back pain, colic, haematuria
Musculoskeletal	Aches and pains, bone pain, arthritis, 'pathological' fractures
Gastrointestinal	Anorexia, nausea, dyspepsia, constipation, abdominal pain
Neurological	Depression, weakness, apathy, lethargy, confusion, psychosis
Cardiovascular	Hypertension

Table 3 Differential diagnoses of hypercalcaemia

Primary hyperparathyroidism	
Malignancy	
haematogenous malignancy	Multiple myeloma, Burkitt lymphoma, Hodgkin lymphoma
solid malignancy with bone metastasis	Breast, lung
solid malignancy without bone metastasis	Hypernephroma, squamous carcinoma
Granulomatous diseases	Sarcoidosis, tuberculosis
Iatrogenic	Thiazide diuretics, lithium, vitamin D intoxication, hypervitaminosis A
Familial hypocalciuric hypercalcaemia	

Hypertension

This is more frequent in patients with primary hyperparathyroidism than in the general population.[54] Efforts to identify a parathyroid-derived hypertensive factor continue. Parathyroidectomy has little or no effect on the severity of the hypertension.

Increased risk of premature death

Although an overall biochemical cure rate of 97% can be achieved in patients undergoing surgery, a study of 896 patients revealed a decreased risk of premature death and better survival for those operated upon at an early stage of disease. It is possible to derive a mathematical function to correlate the estimated hazard for death in relation to gender, age and tumour weight.[41]

Normocalcaemic hyperparathyroidism

Patients with symptoms or complications of primary hyperparathyroidism but presenting with normocalcaemia represent a diagnostic challenge.[64] Most such patients present with a renal calculus and many will have hypercalciuria. They need to be differentiated from those with idiopathic hypercalciuria (increased intestinal Ca^{2+} absorption, diminished tubular resorption of Ca^{2+} resulting in a renal leak or a primary urinary phosphate leak). Identifying patients with normocalcaemic primary hyperparathyroidism is important because surgery should reduce the chance of further stone formation. Failure to consider these other causes and assuming that the patients has normocalcaemic primary hyperparathyroidism will lead to inappropriate neck exploration.

Hypercalcaemic crisis

The severity of clinical manifestations frequently correlates with the degree of hypercalcaemia. Neuromuscular, renal and gastrointestinal manifestations are influenced by the time course of developing hypercalcaemia and intercurrent medical conditions.

Marked dehydration results in anorexia, nausea and vomiting and leads to even more severe hypercalcaemia. Weakness and lethargy lead to immobility, which may accentuate increased bone resorption. Profound mental changes, confusion, cognitive impairment and coma are possible. If untreated, the process evolves to oliguric renal failure, cardiac arrhythmia and death.

Assays for PTH1–84 completely separate individuals with primary hyperparathyroidism (having high or non-inhibited PTH concentrations) from other causes of hypercalcaemia (with low or undetectable PTH levels). As a general rule, the higher the concentrations of plasma calcium, the more likely that malignancy is the underlying cause.

Differential diagnosis of hypercalcaemia

The main differential diagnoses of hypercalcaemia are summarized in Table 3. Other causes that used to be considered but are rare now include: milk-alkali syndrome, immobilization associated with fractures, acute renal failure and other endocrine diseases (thyrotoxicosis, phaeochromocytoma and adrenal crisis).

The majority of patients with acute primary hyperparathyroidism have long-standing hypercalcaemia, large parathyroid adenomas, radiographic evidence of osteitis fibrosa cystica (50%) and a history of nephrolithiasis (60%).[27] Ectopic secretion of PTH has been demonstrated only very rarely (e.g. in ovarian carcinoma).

Investigations used to confirm primary hyperparathyroidism

Biochemical features of primary hyperparathyroidism

These include (i) high total serum calcium (corrected for albumin) or elevated serum ionized calcium; (ii) hypophosphataemia, phosphaturia; (iii) hyperchloraemia and increased chloride:phosphate ratio (see above); (iv) hypercalciuria (>10 mmol/day) is present in >75% of hypercalcaemic patients (excess calcium spillage supports a diagnosis of primary hyperparathyroidism but, more importantly, loss of <2 mmol of calcium per day suggests a diagnosis of familial hypercalcaemic hypocalciuria; this autosomal dominant disease may mimic primary hyperparathyroidism very closely, with normal levels of parathyroid hormone which are judged to be inappropriate in the face of

Table 4 Therapeutic options adapted to the severity of disease[7]

Degree of hypercalcaemia		
Mild (2.6–2.85 mM)	**Moderate (2.85–3.30 mM)**	**Severe(>3.30 mM)**
Symptomatic patients (50%) surgery Asymptomatic patients (50%)· mobilize; keep well hydrated, include moderate amount of calcium in diet; give oestrogens to menopausal women; give oral clodronate	Surgery	Emergency medical treatment followed by surgery

hypercalcaemia. A repeat urinary calcium determination, enquiry into family history and measurement of the serum calcium in first-degree siblings will confirm the correct diagnosis and save the patient an unnecessary neck exploration); (v) increased concentration of intact PTH: high or non-inhibited PTH concentration in the face of hypercalcaemia is diagnostic of primary hyperparathyroidism. Care is required in its interpretation, especially if there is any evidence of renal failure. In this situation the carboxy-terminal, biologically inactive, PTH fragments may accumulate and give a falsely reassuring weight to the diagnosis; (vi) increased serum alkaline phosphatase and increased urinary excretion of cyclic adenosine monophosphate and hydroxyproline can be demonstrated as markers of bone involvement.

Radiological investigations

(i) Parathyroid imaging: the advantage and cost-effectiveness of preoperative localization and unilateral neck exploration in primary hyperparathyroidism are controversial issues. Some surgeons favour such an approach because unilateral exploration may save approximately 30 min of operating time and decrease the risk of damaging the contralateral recurrent laryngeal nerve and normal parathyroid glands.[101] Others report unacceptably high failure rates for unilateral neck exploration compared with a bilateral neck exploration by an experienced surgeon and question the cost-effectiveness of preoperative localizing studies.[43 105]

(ii) Imaging of bone lesions: hand x-ray may demonstrate early subperiostal erosion on the radial aspect of the middle phalanges and, in advanced disease, generalized demineralization is seen, with local cystic destructive lesions, such as 'salt and pepper' skull. Changes in bone density can be studied by ^{125}I bone densitometry, x-ray spectrophotometry or single-photon absorptiometry. Bone mass can be evaluated by single- and dual-photon absorptiometry, quantitative CT and dual-energy x-ray absorptiometry (DEXA scan). In many patients there is an initial rapid loss in bone mass followed by a period of stable disease with little progression at the time of diagnosis of primary hyperparathyroidism.

Treatment of primary hyperparathyroidism

For many years, the management options have been adapted to the severity of primary hyperparathyroidism (Table 4) and surgery was considered clearly recommended for patients with symptomatic primary hyperparathyroidism, for younger patients and for those in whom consistent long-term follow-up could not be assured. The current trend is to recommend parathyroidectomy for all patients with a definite diagnosis of primary hyperparathyroidism (see below).

Medical treatment

Hypercalcaemic crisis treatment involves (i) rehydration: 4–6 litres of fluid are often required to restore normal fluid volumes in the first 24 h. This increases calcium excretion by 25–75 mEq day^{-1} but rarely normalizes serum calcium if used alone; (ii) forced saline diuresis: loop diuretics depress the proximal tubular reabsorption of calcium and can increase urinary calcium excretion by 200–250 mEq day^{-1}. Furosemide (40 mg i.v. every 4 h) should not be initiated until volume repletion has been achieved. The risks of forced diuresis include cardiac decompensation (central venous pressure monitoring is needed for some patients), hypophosphataemia, hypokalaemia and hypomagnesaemia; (iii) antiresorptive agents: bisphophonates (pamidronate, etidronate, clodronate) are now first-line treatment because of their rapid and longer-lasting effect; (iv) calcitonin: salmon, porcine and human calcitonin rapidly decrease the skeletal release of calcium and phosphorus but the effects are temporary and not usually significant.

Dialysis is reserved for patients with renal failure. Peritoneal dialysis can remove 100–500 mEq of calcium in 24 h, and haemodialysis approximately 70 mEq h^{-1}.

Glucocorticoids are not effective in primary hyperparathyroidism but may be useful in treating patients with myeloma, lymphoma or granulomatous diseases (increased vitamin D production by activated macrophages in granulomas) or with vitamin D intoxication. Intravenous phosphate therapy is dramatically effective but is seldom indicated because of serious potential hazards associated with precipitation of calcium phosphate.

Somatostatin may reduce hypercalciuria[58] but in a controlled, prospective, blinded, randomized clinical trial, a single i.v. application of 200 μg of the somatostatin analogue octreotide (SMS 201-995, Sandostatin) failed to induce any significant changes in serum calcium, phosphate, parathyroid hormone, calcitonin or osteocalcin.[40]

The recent cloning of the Ca^{2+} receptor has triggered efforts to develop drugs which could increase the affinity of Ca^{2+} receptor for $[Ca^{2+}]_{ext}$ and thereby potentially correct the biochemical abnormalities in primary hyperparathyroidism. One such compound is NPS R-568, an allosteric modulator of the Ca^{2+} receptor that potentiates the effects of cation agonists on Ca^{2+} receptors.[37] Pharmacological activation of Ca^{2+} receptors *in vivo* with NPS R-568 inhibits PTH secretion. In clinical studies, NPS R-568 inhibited PTH secretion in healthy postmenopausal women. A randomized, placebo-controlled, double-blinded trial concluded that single and increasing doses of NPS R-568 (20–160 mg) inhibit PTH secretion by <70% for <4–8 h in postmenopausal women with mild primary hyperparathyroidism.[87] Clinical trials to establish the therapeutic potential of this Ca^{2+} receptor agonist are in progress. Two years of treatment of a woman with hypercalcaemia secondary to parathyroid carcinoma with NPS R-568 produced no adverse clinical effects and the drug appeared effective in long-term control of hypercalcaemia.[16]

Surgical treatment for primary hyperparathyroidism

Once the biochemical diagnosis is confirmed, neck exploration can be undertaken since the use of imaging techniques provides no benefit in patients with primary hyperparathyroidism attending for first exploration. Patients must be informed about the risk of damage to the recurrent laryngeal nerve (should be <0.5%) and normal parathyroid glands (should be almost zero) and the possibility of failure to identify the parathyroid adenoma (perhaps 1%, due to intrathoracic or ectopic tumour, or wrong diagnosis).

For parathyroid adenomas, because of the possibility of double adenomas, several methods have been proposed to ensure complete excision of the excess PTH source, including measurement of urinary cAMP or rapid intraoperative serum PTH concentrations.[96]

Sporadic multiple gland hyperplasia requires excision of the enlarged glands, leaving the normal sized glands intact,[92] excision of three or three and a half glands has also been recommended.[34]

If parathyroid carcinoma is suspected preoperatively (suggestive features on CT scan or palpable lymphadenopathy), *en bloc* resection offers the best results with central compartment dissection when there is evidence of regional node metastases.

A recent report of 286 patients with parathyroid carcinomas followed for 10 yr concluded that neither tumour size nor lymph node status was a significant prognostic factor.[47] Serum calcium and PTH measurements are postoperative markers of tumour recurrence. Recurrence in the neck or lungs can often be treated by further surgery and, although rarely curative, appears to prolong survival and palliate the symptoms of hypercalcaemia.[98] Radiotherapy is of little use. Mithramycin is a potent hypocalcaemic agent which is often effective for many months; more recently, symptomatic relief has been obtained by using disodium clodronate. The outlook is variable and, as with many endocrine tumours, some patients survive for many years with indolent metastatic disease.

It is now accepted that, for many asymptomatic patients, the time and expense involved in rigorous follow-up outweigh the burden of surgery. Further arguments in favour of parathyroidectomy for patients with absent, minimal or unrecognized symptoms of primary hyperparathyroidism are:[88] (i) subtle physical and psychological changes are only appreciated on restoration of biochemical normality; (ii) there is a risk of developing renal impairment in the long term; (iii) there is a risk of bone loss, which is especially important in elderly females; (iv) hypercalcaemia may contribute to confusion in the elderly; (v) there is a risk of hypercalcaemic crisis in the elderly, especially if there is intercurrent illness, producing dehydration; (vi) the incidence and mortality from cardiovascular disease are greater in untreated patients.

When surgery is contemplated in such patients, the preoperative risk factor profile is altered. These patients are more likely to be receiving antihypertensive medication and frequently have a history of congestive heart disease, ST-segment depression and T-wave abnormalities on ECG, thromboembolic disease, stroke or diabetes mellitus.[55]

Serum calcium need not be checked until 24 h after surgical treatment for primary hyperparathyroidism.[102] Serum PTH concentrations return to within the normal range after 24–48 h; the increased set-point is normalized on the first postoperative day; and the suppression of PTH concentrations during an oral calcium load is normalized on the second postoperative day.

The British Association of Endocrine Surgeons is producing guidelines which will recommend uniform collection of endpoint data for comparative audit, which will include: percentage of patients achieving normocalcaemia at 12 months, recurrent laryngeal nerve injuries (%) and incidence of drug-dependent hypocalcaemia at 12 months. The number of negative operations and reoperative rates will also be measured.

Persistent hyperparathyroidism is the commonest cause of postoperative hypercalcaemia and is defined as hypercalcaemia in the immediate postoperative period or occurring within 1 yr of surgery. Recurrent hyperparathyroidism is defined as hypercalcaemia occurring after a normocalcaemic phase of ⩾1 yr after an operation that identified all four parathyroid glands and removed all abnormal parathyroid tissue.

Secondary hyperparathyroidism

Secondary hyperparathyroidism is the condition in which PTH secretion is increased to compensate for a chronically low concentration of calcium (Table 5) with no intrinsic parathyroid abnormality. Most patients with chronic renal failure develop some degree of parathyroid hyperplasia: the prevalence has been evaluated at 67% using a bone biopsy technique.[57] Largely as a result of improved and early

Table 5 Possible causes of secondary hyperparathyroidism

- Chronic renal failure
- Rickets
  - vitamin D deficiency
  - vitamin D resistance syndromes
  - renal tubular phosphate-wasting disorders
- Osteomalacia
- Malabsorption
- Pseudohypoparathyroidism
- Complication of high-dose phosphate therapy in patients with X-linked hypophosphataemia

medical treatment (calcium and vitamin D replacement therapy), <5% of these patients eventually require parathyroidectomy.[20]

Mechanisms of secondary hyperparathyroidism

In early renal failure, deficient calcitriol synthesis is an important factor but a reduced number of vitamin D receptors[51] or of the newly cloned Ca^{2+}-sensor receptor, may also be present in the parathyroid cells. With advanced chronic renal failure, hyperphosphataemia worsens the condition. Parathyroid cells are resistant to calcitriol because of a reduced density of calcitriol receptors. Finally, uraemia *per se* may not only cause a receptor abnormality in parathyroid cells but may also aggravate the impaired calcaemic response to PTH in the skeleton.[56]

In vivo dynamic tests of parathyroid gland function suggest that calcium-regulated PTH release does not differ with the degree of disease and that set-point abnormalities do not account for excess PTH secretion. Variations in the size of the parathyroid gland may therefore be the major contributor to excessive PTH secretion.[33]

Clinical presentation of secondary hyperparathyroidism

The vast majority of patients are on dialysis and present with a highly variable frequency and severity of symptoms. Patients develop osteitis fibrosa cystica or osteomalacia, which may eventually lead to skeletal deformities or fractures. Physical findings may include a funnel chest deformity and sternal bowing due to rib deformities, and height reduction from kyphosis and vertebral crush fractures. Bone pain occurs primarily in the thoracolumbar spine and lower extremity and is exacerbated by weight bearing, sudden movements and pressure. Subperiosteal bone resorption is seen in <86% of patients, especially in the phalanges, pelvis, distal clavicles, ribs, femur, mandible or skull. The earliest radiographic lesion seen is an irregularity of the radial aspect of the second digit middle phalanx. In a patient maintained on dialysis with appropriate medical treatment, radiographic findings of bone disease should serve as an indication for operation. Osteomalacia is now seen only rarely, thanks to better attention to prevention of aluminium toxicity. Aluminium bone disease must be correctly identified and serum aluminium measurement and scintigraphy may be necessary. The prevalence of aluminium bone disease is decreasing as the use of aluminium-based phosphate binders and antacids is decreasing in favour of calcium salts.

Soft tissue calcification is a frequent manifestation of secondary hyperparathyroidism, affecting 27% of patients at the outset of dialysis and 58% of those who have been dialysis dependent for >5 yr.[68] Calcification may involve vascular and soft tissues, including kidneys (nephrocalcinosis), lungs, heart and skin. A simplistic mechanism for metastatic calcification is crystallization occurring if the serum calcium phosphate product increases above a certain level. Some suggest that high concentrations of the serum calcium phosphate product are an indication for parathyroidectomy.[15]

Calciphylaxis is a rare condition associated with haemodialysis or transplantation, high PTH concentrations and increased serum calcium phosphate product. Patients present with severe calf pain and tenderness with extensive, non-ulcerating, large, hard and tender subcutaneous plaques. These painful, violaceous, mottled cutaneous lesions progress to skin and subcutaneous necrosis, deep non-healing ulcers and gangrene. The lesions are reticular in pattern, appear characteristically on fingers and toes (although the forearms, arms, trunk, buttocks, thighs and legs may also be involved) and may be very large (up to 20 cm). This severe complication can threaten digits, limbs or the patient's life. Calcium deposition can be confirmed radiologically and by bone scanning. The condition is not uncommon and can occur in predialysis patients.[26]

Pruritus can be severe, intractable and disabling and has been attributed to increased calcium concentrations in the skin. This usually improves after parathyroidectomy.

Patients may also tire easily and have muscle weakness, proximal myopathy and peptic ulcer.

'Cardiotoxicity' of PTH

A 5 yr longitudinal echocardiographic study of 52 patients dependent on haemodialysis demonstrated that one of the best clinical predictors for the presence of left ventricular hypertrophy was an increased PTH concentration. A possible direct effect is mediated by specific receptors for PTH in the cardiomyocytes and by a permissive role on activation of interstitial cells in the heart. A raised calcium phosphate product leads to myocardial and valve calcification and to cardiac dysfunction. An increased cytosolic calcium concentration in the cardiomyocytes in uraemic patients lessens myocardial performance.[94]

Laboratory diagnoses of secondary hyperparathyroidism

Hyperphosphataemia is accompanied by normocalcaemia or hypocalcaemia; increased concentrations of intact PTH are decisive for diagnosis and exclude the diagnostic confusion created by measuring the carboxy-terminal fragment of PTH (as in previous assays), which accumulates as a result of decreased renal clearance; increased alkaline phosphatase demonstrates the severity of bone disease; serum levels of vitamin D are monitored to confirm adequate substitution; serum aluminium concentration is checked to exclude aluminium toxicity as a cause of bone disease.

Medical treatment of secondary hyperparathyroidism

The goals of such treatment are to maintain calcium and phosphate concentrations close to normal levels, to suppress PTH secretion and ameliorate pre-existing bone disease. The methods available include the following.

(i) Dietary phosphate restriction (<1000 mg 24 h^{-1}) can be coupled with phosphate-binding agents to reduce phosphate absorption from the intestinal tract. Calcium carbonate is preferred to aluminium hydroxide and the dose is adapted to the phosphate content of foods.

(ii) Daily calcium intake of ≥1500 mg is necessary and can be achieved using oral supplementation. If the patient is still hypocalcaemic, calcium may be added to the dialysis fluid to achieve normocalcaemia.

(iii) Long-term treatment with calcium α-ketoglutarate (approximately 4.5 g day^{-1}) normalizes secondary hyperparathyroidism by simultaneously binding phosphate and correcting the calcium:phosphate ratio in serum without vitamin D treatment.[104]

(iv) Routine vitamin D supplementation is started before a patient becomes dependent on dialysis. The risks of vitamin D treatment include the development of hypercalcaemia and persistent hyperphosphataemia. Calcitriol concentrations should be measured during treatment with vitamin D. Weekly intravenous bolus administration is safe and cost-effective.

(v) Aluminium toxicity can be treated successfully with desferroxamine.

(vi) Pruritus is ameliorated by charcoal haemoperfusion in conjunction with standard haemodialysis.

(vii) The use of disphosphonates in the treatment of secondary hyperparathyroidism is being evaluated. These drugs have a high affinity for hydroxyapatite, inhibit osteoclast mediated bone-resorption, reduce bone resorption and decrease calcium and phosphate concentrations, but PTH concentrations increase.

(viii) PTH removal during continous ambulatory peritoneal dialysis (CAPD) is greater than with haemodialysis, but CAPD has the disadvantage of greater protein losses. Vitamin D and its binding protein are lost in peritoneal dialysate.

(ix) In an experimental model of secondary hyperparathyroidism, chronic administration of the Ca^{2+} receptor agonist NPS R-568 inhibited PTH synthesis and secretion and decreased parathyroid cell volume.[31]

Medical therapy fails in 5–10% of patients on long-term dialysis, and surgery becomes necessary.

Surgical treatment for secondary hyperparathyroidism

Indications for operation are based in part on the knowledge that bone and joint pain, pruritus and malaise are likely to improve in about 80% of patients after parathyroidectomy. When this treatment is offered, patients must be informed about the potential risks (bleeding, recurrent hyperparathyroidism, hypoparathyroidism and injury to the recurrent laryngeal nerves).

Patients should undergo dialysis within 1 day of surgery and then 48 h postoperatively or as needed. The risk of bleeding should be kept in mind since heparin is used during haemodialysis and platelets are dysfunctional in severely uraemic patients. Preoperative vitamin D treatment should continue since it decreases the chance of postoperative hypocalcaemia.

The typical histopathological findings are asymmetric enlargement, nodularity and increased numbers of oxyphil cells. Nodular hyperplasia indicates a more aggressive proliferation than diffuse hyperplasia.[95]

Severe postoperative hypocalcaemia may occur as a result of 'hungry bone syndrome', hypomagnesaemia and failure of parathyroid grafts. Oral supplementation (<6 g of elemental calcium can be given daily) suffices for mild symptoms but severe hypocalcaemia requires intravenous calcium and magnesium.

Technical options

A small viable portion of one parathyroid gland (the one showing diffuse hyperplasia on frozen section) is left *in situ* (subtotal parathyroidectomy) or is used as an autograft in the forearm (total parathyroidectomy). If all four glands are not found in the 'classical' locations, the retro-oesophageal space, superior thyroid pedicles and the area along the carotid sheath and thymus should be explored. Median sternotomy should not be performed as part of the initial operation. Pathology reports, postoperative PTH and calcium concentrations and the clinical response should influence further decisions about localization studies in anticipation of re-exploration. Recently, total parathyroidectomy has become a preferred option.

The relative merits of subtotal and total parathyroidectomy plus autograft are still controversial. Subtotal parathyroidectomy involves resection of three and a half glands and approximately 50 mg viable tissue is left *in situ* with preserved vascularity. The disadvantage of this method is that a second operation in the neck is needed in the event of persistent or recurrent hyperparathyroidism. In total parathyroidectomy plus autotransplantation, a small gland that shows predominantly diffuse hyperplasia on frozen section is selected for autografting in the forearm flexor muscle mass and some fragments can be cryopreserved. Primary graft failure is extremely rare. Parathyroid graft function can be further evaluated by measuring PTH gradients between grafted and non-grafted antecubital venous samples.

Some recommend subtotal parathyroidectomy without remnant implantation as a safe and durable intervention for secondary hyperparathyroidism and following renal transplantation.[75] In one series of 91 patients, this intervention was associated with an acceptably low recurrence rate (4.1% at 1 yr and 11.7% at 20 yr). Overall hospital mortality was 3% (3/91) and none of the deaths was directly attributable to parathyroidectomy.[79]

Tertiary hyperparathyroidism

Tertiary HPT is the condition in which parathyroid hyperplasia progresses to autonomous hypersecretion so that excessive PTH secretion continues despite correction of the underlying renal disease. It is estimated to occur in 25–50% of patients based on calcium concentrations, but PTH concentrations and bone biopsies suggest a prevalence of <70% soon after renal transplant. Only few require operation and about 60% of these patients become normocalcaemic within 12 months.

After transplantation, patients usually present with less severe disease, have better normalization of biochemical variables after parathyroidectomy and rarely develop recurrent hyperparathyroidism. Both total parathyroidectomy with autotransplantation and subtotal parathyroidectomy result in good control of renal hyperparathyroidism with excellent improvement of symptoms.[67]

Familial syndromes including hyperparathyroidism

Multiple endocrine neoplasia type 1

MEN1 is a rare autosomal dominant familial cancer syndrome with a prevalence estimated to be between one in 10 000 and one in 100 000. Affected individuals develop various combinations of tumours in parathyroid glands, enteropancreatic endocrine tissues and the anterior pituitary, with 94% penetrance by the age of 50 yr. Less commonly associated tumours include foregut carcinoids, lipomas, thyroid adenomas, adrenocortical adenomas, angiomyolipomas and spinal cord ependymomas (reviewed in 62).

Hyperparathyroidism is the most common lesion in MEN1, with an estimated 90% prevalence in autopsy and screening studies. It is usually the first abnormality detected on screening and the parathyroid glands are almost always hyperfunctional by the time islet cells or pituitary involvement becomes clinically evident. Patients are first detected in their teens; by the age of 40 yr, >95% of patients have hypercalcaemia. The clinical picture is similar to sporadic hyperparathyroidism, apart from the symptoms, which may relate to other tumours (e.g. peptic ulcer caused by the presence of a gastrinoma). Characteristically, multigland parathyroid hyperplasia is found, but one or more glands can be macro- and microscopically normal.

In 1988, *MEN1* was mapped to chromosome position 11q13 by linkage analysis.[52] In 1997, two independent groups cloned the *MEN1* gene and showed that it encodes a ubiquitously expressed 610 amino acid protein, referred to as MENIN.[14 22] Over 40 mutations of the *MEN1* gene have been identified so far[4] and are likely to inactivate the MENIN function, which is consistent with the proposal that MEN1 results from inactivating mutations of a tumour suppressor gene.

MEN2

MEN2 is an autosomal dominant syndrome with incomplete penetrance and varying expression. MEN2A associates medullary thyroid carcinoma with a phaeochromocytoma (in 50% of patients) and hyperparathyroidism (in 15–30% of patients). In MEN2B there is a general (not absolute) lack of parathyroid involvement. General clinical features of MEN2 syndromes have been reviewed recently.[62] Hyperparathyroidism develops in 10–25% of patients, is characterized by mild hypercalcaemia (usually asymptomatic); the median age at diagnosis is 38 yr. Biochemical screening involves annual measurement of serum calcium concentrations followed by measurement of intact PTH only in hypercalcaemic patients. Generalized but asymmetric parathyroid hyperplasia is the most common histological abnormality.

MEN2 is a familial cancer syndrome arising from germline point mutations in the *RET* proto-oncogene located on chromosome 10 (at position 10q11.2). Multiple *RET* mutations have been described and are currently being collected by a *RET* Mutation Consortium for confirmation of a predicted genotype–phenotype correlation.[66] The *RET* proto-oncogene encodes a cell-surface glycoprotein related to the family of receptor tyrosine kinases[70] and is normally expressed in derivatives of the neural crest, including C cells, chromaffin and parathyroid cells.[71]

Familial isolated hyperparathyroidism

Familial isolated hyperparathyroidism is a rare autosomal dominant disorder which occurs as a genetically and clinical distinct entity. More than 30 kindred have been reported to display primary hyperparathyroidism with no evidence of other associated endocrinopathies. A study of 37 members of such a family has shown no linkage between familial isolated hyperparathyroidism and MEN1 or MEN2A.[50]

Other familial syndromes involving parathyroid disease are very rare and have been reviewed elsewhere.[62]

Relevance of parathyroid disease for anaesthesia

ECG changes

Increases in $[Ca^{2+}]_{ext}$ enhance myocardial contractility. When large amounts of calcium are infused into experimental animals, the heart relaxes less during diastole and eventually stops in systole (calcium rigor). In clinical conditions, however, the plasma calcium concentration is rarely high enough to affect the heart. On ECG, hypocalcaemia causes prolongation of the ST segment and QT interval but hypercalcaemia has less specific effects.

Drug interactions

Hypercalcaemia enhances digitalis toxicity so care should be taken in the preoperative assessment of older patients who may be taking or require this drug.

Recurrent laryngeal nerve injuries

During extubation, the anaesthetist should check the position of the vocal cords. If they are in the normal position, this confirms that the recurrent laryngeal nerves have not been damaged during dissection of the parathyroid glands. The recurrent laryngeal nerves supply all the muscles of the larynx except the cricothyroid (which is innervated by the external laryngeal nerve) and the mucous membrane below the vocal cords. With complete recurrent laryngeal nerve paralysis, the vocal fold takes a half-abducted position, there is vibration of the fold and stridor and the voice becomes hoarse. With partial lesions of the recurrent laryngeal nerve, the vocal fold takes an adducted position. From the point of view of airway obstruction, a partial lesion is more serious than a complete lesion; a bilateral partial lesion is life-threatening.

References

1 Albright F, Baird PC, Cope O *et al.* Studies of the physiology of the parathyroid glands. IV. Renal complications of hyperparathyroidism. *Am J Med Sci* 1934; **187**: 49–65

2 Anast CS, Winnacker JL, Forte LR, Burns TW Impaired release of parathyroid hormone in magnesium deficiency. *J Clin Endocrinol Metab* 1976; **42**: 707–17

3 Arnold A, Staunton CE, Kim HG *et al.* Monoclonality and abnormal PTH genes in parathyroid adenomas. *New Engl J Med* 1988; **318**: 658–62

4 Bassett JDH, Forbes SA, Pannett AAJ *et al.* Characterisation of mutations in patients with multiple endocrine neoplasia type 1. *Am J Hum Genet* 1988; **62**: 232–44

5 Bates S, Peters G. Cyclin D1 as a cellular proto-oncogene. *Sem Cancer Biol* 1995; **6**: 73–82

6 Bauer W, Federman DD. Hyperparathyroidism epitomized: the case of Captain Charles E. Martell. *Metabolism* 1962; **11**: 21–9

7 Bilezikian JP. Management of hypercalcaemia. *J Clin Endocrinol Metab* 1993; **77**. 1445–9

8 Boucher A, D'Amour P, Hamel L *et al.* Estrogen replacement decreases the set point of parathyroid hormone stimulation of calcium in normal postmenopausal women. *J Clin Endocrinol Metab* 1989; **68**: 831–6

9 Brown EM. Four parameter model of the sigmoidal relationship between PTH release and extracellular calcium concentration in normal and abnormal parathyroid tissue. *J Clin Endocrinol Metab* 1983; **56**: 572–81

10 Brown EM. Extracellular calcium sensing, regulation of parathyroid cell function and role of Ca^{2+} and other ions as extracellular (first) messengers. *Physiol Rev* 1991; **71**: 371–411

11 Brown EM, Gamba G, Riccardi D *et al.* Cloning and characterisation of an extracellular Ca^{2+}-sensing receptor from bovine parathyroid. *Nature* 1993; **366**: 575–80.

12 Brown EM, Segre GV, Goldring SR. Serpentine receptors for parathyroid hormone, calcitonin and extracellular calcium. *Baillière's Clin Endocrinol Metab* 1996, **10**: 123–61

13 Carling T, Kindmark A, Hellman P *et al.* Vitamin D receptor genotypes in primary hyperparathyroidism. *Nature Med* 1995; **1**: 1309–11

14 Chandrasekharappa SC, Guru SC, Manickam P *et al.* Positional cloning of the gene for multiple endocrine neoplasia type 1. *Science* 1997; **276**: 404–8

15 Clark O, Siperstein A. Hypercalcaemic syndrome: hyperparathyroidism. In: Freisen S, Thompson N, eds. *Surgical Endocrinology—Clinical Syndromes*, 2nd edn. Philadelphia· J. B. Lippincott, 1990, 311–12

16 Collins MT, Skarulis MC, Bilezikian JP, Silverberg SJ, Spiegel AM, Marx SJ. Treatment of hypercalcaemia secondary to parathyroid carcinoma with a novel calcimimetic agent. *J Clin Endocrinol Metab* 1998; **83**: 1083–8

17 Collip JB. The extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium. *J Biol Chem* 1925; **63**: 395–438

18 Cryns VL, Rubio MP, Thor AD *et al.* p53 abnormalities in human parathyroid carcinoma. *J Clin Endocrinol Metab* 1994; **78**: 1320–24

19 Cryns VL, Thor A, Xu HJ *et al.* Loss of the retinoblastoma tumor-suppressor gene in parathyroid carcinoma. *New Engl J Med* 1994; **330**: 757–61

20 Demeure M, McGee D, Wilkes W *et al.* Results of surgical treatment for hyperparathyroidism associated with renal disease. *Am J Surg* 1990; **160**: 337–40

21 Elvius M, Lagrelius A, Nygren A, Alveryd A, Christensson TAT, Nordenstrom J. Seventeen year follow-up study of bone mass in patients with mild asymptomatic hyperparathyroidism some of whom were operated on. *Eur J Surg Acta Chirurg* 1995; **161**: 863–9

22 The European Consortium on MEN1. Identification of the multiple endocrine neoplasia type 1 (MEN1) gene *Hum Mol Genet* 1997; **6**: 1117–83

23 Falchetti A, Bale A, Amorosi A. Progression of uremic hyperparathyroidism involves allelic loss on chromosome 11. *J Clin Endocrinol Metab* 1993; **76**: 139–44

24 Farndon JR, Geraghty JM, Dilley WG, Handwerger S, Leight GS. Serum gastrin, calcitonin, and prolactin as markers of multiple endocrine neoplasia syndromes in patients with primary hyperparathyroidism. *World J Surg* 1987; **11**: 252–7

25 Farndon JR, Routledge PA *et al.* Beta-adrenergic effects on PTH release. *Br J Surg* 1981; **68**: 77–83

26 Fine A, Fleming S, Leslie W. Calciphylaxis presenting with calf pain and plaques in four continuous ambulatory peritoneal dialysis patients and in one predialysis patient. *Am J Kidney Dis* 1995; **25**: 498–502

27 Fitzpatrick LA, Bilezikian JP. Acute primary hyperparathyroidism. *Am J Med* 1987; **82**: 275–82

28 Friedman E, Sakaguci K, Bale AE *et al.* Clonality of parathyroid tumours in familial MEN type 1. *New Engl J Med* 1989; **321**: 213–18

29 Friedman E, Bale AE, Marx SJ *et al* Genetic abnormalities in parathyroid adenomas. *J Clin Endocrinol Metab* 1990; **71**: 293–7

30 Garrett JE, Capuano IV, Hammerland LG *et al.* Molecular cloning and functional expression of human parathyroid calcium receptor cDNAs. *J Biol Chem* 1995; **270**: 12919–25

31 Garrett JE, Steffey ME, Nemeth EF. The calcium receptor agonist R-568 suppresses PTH mRNA levels in cultured bovine parathyroid cells. *J Bone Min Res* 1995; **10**: S387 (M539)

32 Gilmour JR The normal histology of the parathyroid glands. *Pathol Bacteriol* 1937; **45**: 507–22 and **48**: 187–222

33 Goodman WG, Belin T, Gales B, Juppner H, Segre GV, Salusky IB. Calcium-regulated parathyroid hormone release in patients with mild or advanced secondary hyperparathyroidism. *Kidney Int* 1995; **48**: 1553–8

34 Grant CS, Weaver A. Treatment of primary parathyroid hyperplasia: representative experience at Mayo Clinic. *Acta Chirurg Austr* 1994; **26** (Suppl 112): 41–4

35 *Gray's Anatomy* (Bannister LH, Berry MM, Collins P *et al.* eds). New York: Churchill Livingstone, 1995; 17

36 Hakim JP, Levine MA. Absence of p53 point mutations in parathyroid adenoma and carcinoma. *J Clin Endocrinol Metab* 1994; **78**: 103–6

37 Hammerland LG, Garrett JE, Hung BCP, Levinthal L, Nemeth EF. Allosteric activation of the Ca^{2+} receptor expressed in *Xenopus laevis* oocytes by NPS-467 R NPS-568. *Mol Pharmacol* 1998; **53**: 1083–8

38 Hanson AM. Parathyroid preparations. *Milit Surg* 1923; **53**: 554–60, 701–18

39 Harms HM, Schlinke E, Neubauer O. Pulse amplitude and frequency modulation of parathyroid hormone in primary hyperparathyroidism. *J Clin Endocrinol Metab* 1994; **78**: 53–7

40 Hasse C, Zielke A, Bruns C *et al.* Influence of somatostatin to biochemical parameters in patients with primary hyperparathyroidism. *Exp Clin Endocrinol Diab* 1995; **103**: 391–7

41 Hedback G, Oden A, Tissel LA. Parathyroid adenoma weight and the risk of death after treatment for primary hyperparathyroidism. *Surgery* 1995; **117**: 134–9

42 Heinrich G, Kronenberg HM, Potts JT, Habener JF. Gene encoding parathyroid hormone—nucleotide sequence of the rat gene and deduced amino acid sequence of rat preproparathyroid hormone. *J Biol Chem* 1984; **259**: 3320–29

43 Hewin DF, Brammar TJ, Kabala J, Farndon JR Role of preoperative localization in the management of primary hyperparathyroidism. *Br J Surg* 1997; **84**: 1377–80

44 Hjalm G, Murray E, Crumley G *et al.* Cloning and sequencing of human gp330, a Ca^{2+}-binding receptor with potential intracellular signalling properties. *Eur J Biochem* 1996; **239**: 132–7

45 Ho C, Conner D, Pollak M *et al.* A mouse model of human familial hypercalcaemia and neonatal severe hyperparathyroidism. *Nature Genet* 1995; **11**: 389–94

46 Hosokawa Y, Pollak MR, Brown EM *et al* The extracellular calcium-sensing receptor gene in human parathyroid tumours. *J Clin Endocrinol Metab* 1995; **80**: 3107–10

47 Hundahl SA, Fleming ID, Fremgen AM, Menck HR. Two hundred and eighty-six cases of parathyroid carcinoma treated in the US between 1985–1995: a National Cancer Data Base Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer*, **86**: 538–44

48 Joborn C, Ljunghall S, Larssan K *et al.* Skeletal responsiveness to parathyroid hormone in healthy females: relationship to menopause and oestrogen replacement. *Clin Endocrinol* 1991; **34**: 335–9

49 Juhlin C, Klareskog L, Nygren P *et al.* Hyperparathyroidism is associated with reduced expression of a parathyroid calcium receptor mechanism defined by monoclonal antiparathyroid antibodies. *Endocrinology* 1988; **122**: 2999–3001

50 Kassem M, Zhang X, Brask S *et al.* Familial isolated primary hyperparathyroidism. *Clin Endocrinol* 1994; **41**: 415–20

51 Korkor AB. Reduced binding of [^{3}H]-1,25-dihydroxyvitamin D3 in the parathyroid glands of patients with chronic renal failure. *New Engl J Med* 1987; **316**: 1573–7

52 Larsson C, Skogseid K, Oberg K, Nakamura Y, Nordenskjold M. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. *Nature* 1988, **332**: 85–7

53 LeDouarin N. *The Neural Crest.* Cambridge: Cambridge University Press, 1984.

54 Lind L, Ljunghall S. Parathyroid hormone and blood pressure—is there a relationship? *Nephrol Dial Transplant* 1995; **10**: 450–51

55 Lind L, Ljunghall S. Pre-operative evaluation of risk factors for complications in patients with primary hyperparathyroidism. *Eur J Clin Invest* 1995; **25**: 955–8

56 Llach F. Secondary hyperparathyroidism in renal failure: The trade-off hypothesis revisited. *Am J Kidney Dis* 1995; **25**: 663–79

57 Llach F, Felsenfeld A, Coleman M *et al.* Renal osteodistrophy in 131 unselected hemodialysis patients. *Kidney Int* 1984; **25**: 187

58 Lucarotti ME, Hamilton JA, Farndon JR. Somatostatin and primary hyperparathyroidism. *Br J Surg* 1994; **81**: 1141–3

59 Lundgren S. Hjalm G, Hellman P *et al.* A protein involved in calcium sensing of the human parathyroid and placental cytotrophoblast cells belongs to the LDL-receptor protein superfamily. *Exp Cell Res* 1994; **212**: 344–50

60 Mandl F. Therapeutischer Versuch bein einem Fall von Ostitis fibrosa generalisata mittles. Exstirpation eines Epithelkorperchentumors. *Wien Klin Wochenschr Zentral* 1926; **53**: 260–64

61 Mansberger AR Jr, Wei JP. Surgical embryology and anatomy of the thyroid and parathyroid glands. *Surg Clin N Am* 1993; **73**: 727–46

62 Mihai R, Farndon JR. Familial endocrine disease—genetics and early treatment. In: Farndon JR ed. *A Companion to Specialist Surgical Practice: Breast and Endocrine Surgery.* London: W. B. Saunders, 1997: 113–42

63 Mihai R, Lai T, Schofield G, Farndon JR. Thimerosal increases the responsiveness of the calcium receptor in human parathyroid and rMTC6-23 cells. *Cell Calcium* 1999; **26**: 95–102

64 Monchik JM. Presidential address. Normocalcemic hyperparathyroidism. *Surgery* 1995; **118**: 917–23

65 Motokura T, Bloom T, Kim HG *et al.* A novel cyclin encoded by a bcl1-linked candidate oncogene. *Nature* 1991; **350**: 512–15

66 Mulligan LM, Marsh DJ, Robinson BG *et al.* Genotype–phenotype correlation in MEN2: report of the International *RET* Mutations Consortium. *J Intern Med* 1995; **238**: 343–6

67 Neonakis E, Wheeler MH, Krishnan H, Coles GA, Davies F, Woodhead JS. Results of surgical treatment of renal hyperparathyroidism. *Arch Surg* 1995; **130**: 643–8

68 Nichols P, Owen JP, Ellis HA *et al.* Parathyroidectomy in chronic renal failure: a nine year follow up study. *Q J Med* 1990; **77**: 1175–93

69 Owen R. On the anatomy of the Indian rhinoceros (*Rh. unicornis*). *Trans Zool Soc Lond* 1862; **4**: 31–58

70 Pasini B, Ceccherini I, Romeo G. *RET* muations in human disease. *Trends Genet* 1996; **12**: 138–44

71 Pausova Z, Soliman E, Amizuka N *et al.* Expression of the *RET* protooncogene in hyperparathyroid tissue: implications in the pathogenesis of the parathyroid disease *J Bone Min Res* 1995; **10**: 249

72 Pearce SHS, Bai M, Quinn SJ, Kifor O, Brown EM, Thakker RV. Functional characterization of calcium-sensing receptor mutations expressed in human embryonic kidney cells. *J Clin Invest* 1996; **98**. 1860–66

73 Pearse AGE. Genesis of neuroendocrine system. In: Friesen SR, Thompson NW, eds. *Surgical Endocrinology—Clinical Syndromes*, 2nd edn Philadelphia: J. B. Lippincott, 1990: 15–21

74 Potts JT, Bringhurst FR, Gardella T *et al.* Parathyroid hormone: physiology, chemistry, biosynthesis, secretion, metabolism and mode of action. In: *De Groot Textbook of Endocrinology*, 1995: 920–66

75 Punch JD, Thompson NW, Merion RM *et al* Subtotal parathyroidectomy in dialysis-dependent and post-renal transplant patients: A 25-year single-center experience. *Arch Surg* 1995; **130**: 538–43

76 Riccardi D, Park J, Lee WS *et al.* Cloning and functional expression of a rat kidney extracellular calcium/polyvalent cation-sensing receptor. *Proc Natl Acad Sci USA* 1995; **92**: 131–5

77 Rodan GA, Fleish HA. Bisphosphonates: mechanism of action. *J Clin Invest* 1996; **97**: 2692–6

78 Rosenberg CL, Kim HG, Shows TB, Kronenberg HM *et al.* Rearrangement and overexpression of D11S287E, a candidate oncogene on chromosome 11q13 in benign parathyroid tumors. *Oncogene* 1991; **6**: 449–53

79 Rothmund M, Wagner P, Schark C Subtotal parathyroidectomy vs total parathyroidectomy and autotransplantation in secondary hyperparathyroidism—a randomised trial. *World J Surg* 1991; **15**. 745–50

80 Russell J, Bar A, Sherwood LM, Hurwitz S. Interaction between calcium and 1,25-dihydroxyvitamin D3 in the regulation of preproparathyroid hormone and vitamin D receptor messenger ribonucleic acid in avian parathyroids. *Endocrinology* 1993; **132**: 2639–44

81 Samuels MH, Veldhuis JD, Cawley C *et al.* Pulsatile secretion of parathyroid hormone in normal young subjects assessment by deconvolution analysis. *J Clin Endocrinol Metab* 1993, **77**: 339–403

82 Sandstrom I. Om en ny kortel hos menniskan och atskilliga daggdjur. *Uppsala Lakaref Forhande* 1880; **15**: 441–71

83 Schmitt CP, Schaefer F, Bruch A *et al.* Control of pulsatile and tonic parathyroid hormone secretion by ionized calcium. *J Clin Endocrinol Metab* 1996; **81**: 4236–43

84 Schneider H, Feyen JH, Seuwen K, Movva NR. Cloning and functional expression of a human parathyroid hormone receptor. *Eur J Pharmacol* 1993; **246**: 149–55

85 Schneider AB, Gierlowski TC, Shore-Freedman E, Stovall M, Ron E, Lubin J. Dose–response relationships for radiation-induced hyperparathyroidism. *J Clin Endocrinol Metab* 1995; **80**: 254–7

86 Scholz DA, Purnell DC. Asymptomatic primary hyperparathyroidism. 10-year prospective study *Mayo Clin Proc* 1981; **56**: 473–8

87 Silverberg SJ, Bone III HG, Marriott TB et *al.* Short-term inhibition of parathyroid hormone secretion by a calcium-receptor agonist in patients with primary hyperparathyroidism. *New Engl J Med* 1997; **337**: 1506–10

88 Stevenson JC, Lynn JA. Time to end a conservative treatment for mild hyperparathyroidism. *Br Med J* 1988; **296**· 1016–17

89 Sugimoto T, Brown AJ, Ritter C *et al.* Combined effects of dexamethasone and 1,25 dihydroxyvitamin D3 on parathyroid hormone secretion in cultured bovine parathyroid cells *Endocrinology* 1989; **125**: 638–641

90 Tahara H, Smith AP, Gaz RD, Cryns VL, Arnold A Genomic localization of novel candidate tumor suppressor gene loci in human parathyroid adenomas. *Cancer Res* 1996; **56**: 599–605

91 Thakker RV, Bouloux P, Wooding C *et al.* Association of parathyroid tumours in MEN type 1 with loss of alleles on chromosome 11. *New Engl J Med* 1989, **321**· 218–24

92 Thompson NW, Sandelin K. Primary hyperparathyroidism caused by multiple gland disease (hyperplasia) long-term results in familial and sporadic cases. *Acta Chirurg Austr* 1994; **26** (Suppl 112): 44–7

93 Thomson DB, Samowitz WS, Odelberg S *et al.* Genetic abnormalities in sporadic parathyroid adenomas: loss of heterozygosity for chromosome 3q markers flanking the calcium receptor locus *J Clin Endocrinol Metab* 1995; **80** 3377–80

94 Timio M. Cardiotoxicity of parathyroid hormone in chronic renal failure. *Ital J Min Electrolyte Metab* 1995; **9**· 119–24

95 Tominaga Y, Sato K, Tanaka Y, Numano M, Uchida K, Takagi H Histopathology and pathophysiology of secondary hyperparathyroidism due to chronic renal failure *Clin Nephrol* 1995; **44** (Suppl 1)· S42–7

96 Tommasi M, Brocchi A, Benucci A *et al.* Intraoperative fall in plasma levels of intact parathyroid hormone in patients undergoing parathyroid adenomectomy *Int J Biol Markers* 1995, **10**: 206–10

97 Trydal T, Varhaug JE, Myking A *et al.* Serum vitamin D metabolites and calcitriol receptor concentration in parathyroid tissue in primary hyperparathyroidism. *Acta Endocrinol* 1992; **127**: 407–12

98 Vetto JT, Brennan MF, Woodruf J, Burt M. Parathyroid carcinoma: diagnosis and clinical history. *Surgery* 1993; **114**. 882–92

99 Weaver CA, Gordon DF, Kissil MS, Mead DA, Kemper B Isolation and complete nucleotide sequence of the gene for bovine parathyroid hormone *Gene* 1984; **28**: 319–29

100 Weber CJ, Marangos PJ, Richardson S *et al* Presence of neuron-specific enolase and somatostatin in human parathyroid tissues *Surgery* 1985, **98**: 1008–12

101 Wei JP, Burke GJ. Analysis of savings in operative time for primary hyperparathyroidism using localization with technetium 99m sestamibi scan. *Am J Surg* 1995; **170**· 488–91

102 Wong WK, Wong NA, Farndon JR. Early postoperative plasma calcium concentration as a predictor of the need for calcium supplement after parathyroidectomy. *Br J Surg* 1996, **83**: 532–4

103 Zabel M, Surdyk J, Biela-Jacek I. Immunohistochemical study of the distribution of S-100 protein in the parathyroid glands of rats and guinea pigs *Histochemistry* 1986; **86**: 97–9

104 Zimmermann E, Wassmer S, Steudle V. Long-term treatment with calcium-alpha-ketoglutarate corrects secondary hyperparathyroidism. *Min Electrolyte Metab* 1996, **22**: 196–9

105 Zmora O, Schachter PP, Heyman Z *et al.* Correct preoperative localization: Does it permit a change in operative strategy for primary hyperparathyroidism? *Surgery* 1995; **118**: 932–5

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Phaeochromocytoma—recent progress in its management

C. Prys-Roberts

Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary, Bristol BS2 8HW, UK

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Phaeochromocytoma is a rare tumour arising from chromaffin cells in the adrenal medulla or in other paraganglia of the sympathetic nervous system.[57] The name, meaning 'dusky-coloured tumour', was first used by Pick[74] in 1912 although the tumour had been recognized earlier by von Frankel.[25] Successful surgery for excision of phaeochromocytoma was first performed by Roux (1926) and Mayo (1927).[101] The tumour can exist sporadically or in conjunction with other endocrine tumours in the multiple endocrine neoplasm (MEN) series.[27 50 85 87] Patients present with a variety of symptoms which reflect excessive secretion of norepinephrine, epinephrine or dopamine into the circulation. Patients with predominantly norepinephrine-secreting tumours present with hypertension, often severe and refractory to conventional therapy. Patients with predominantly epinephrine- (and dopamine-) secreting tumours present with a variety of symptoms, usually episodic, such as tachycardia with palpitations, panic attacks and feelings of doom. Few medical conditions pose such a severe but unpredictable threat to the patient's life, and it is therefore essential, as soon as a diagnosis is made, to commence medical therapy to inhibit the end-organ actions of the relevant catecholamines, pending surgical excision.

There has been an increasing tendency for patients with a definitive diagnosis of phaeochromocytoma to be referred to specialist endocrine surgeons, who in turn work with anaesthetists with specialist experience, and this can only be beneficial for such patients. Few anaesthetists have substantial experience of treating patients with phaeochromocytoma, but the review by Hull in this journal was a landmark,[37] reflecting his considerable experience in dealing with the diagnosis, preoperative preparation and anaesthetic management of the condition. In the 13 yr since that review was published, a number of new developments have occurred in various aspects of the medical, surgical and anaesthetic treatment of patients with these rare tumours. With the exception of historical landmark papers, I have restricted references to those which have appeared since 1980 and, generally, I have not duplicated those quoted by Hull.[37]

Histological and genetic origins of phaeochromocytoma

Cells embryologically derived from the neuroblasts of the neural crest develop in a variety of endocrine and non-endocrine tissues, where they secrete polypeptide hormones or hormone precursors (Fig. 1). These cells have a common cytochemical function in that they take up chemical precursors which they decarboxylate to produce a variety of biologically active amines; it is for this reason they have been classified as APUD cells (amine and amine precursor uptake and decarboxylation).[6 71] Chromosomal mutational changes in the *RET* proto-oncogene cause neoplastic changes in these cells,[65 66] resulting in the formation of tumours which may occur sporadically or as part of a familial syndrome. Phaeochromocytomas arise predominantly from chromaffin cells in the adrenal medulla, although about 6% occur in other tissues of neuroectodermal origin such as the paraganglial cells of the sympathetic nervous system, including those of the organ of Zuckerkandl.[12 57] There have been sporadic reports of phaeochromocytoma arising in the heart or pericardium.[45 80 89]

The majority (90%) of phaeochromocytomas occur sporadically and are benign.[57] In about 10% of patients with phaeochromocytoma the adrenal tumour is part of a familial disorder such as the MEN syndromes, von Recklinghausen disease or von Hippel–Lindau syndrome.[61]

MEN syndromes

The term MEN describes a series of syndromes which were originally identified as familial by the study of specific kindreds,[65] and which are now known to be genetically linked.[61]

MEN 1

For completeness it is worth describing Wermer's syndrome (MEN 1),[102] a rare autosomal dominant disease which has been widely studied in nearly 2000 descendants of an English migrant to Tasmania.[84] It consists of tumours of the parathyroid glands, pancreatic islets (insulinomas) and

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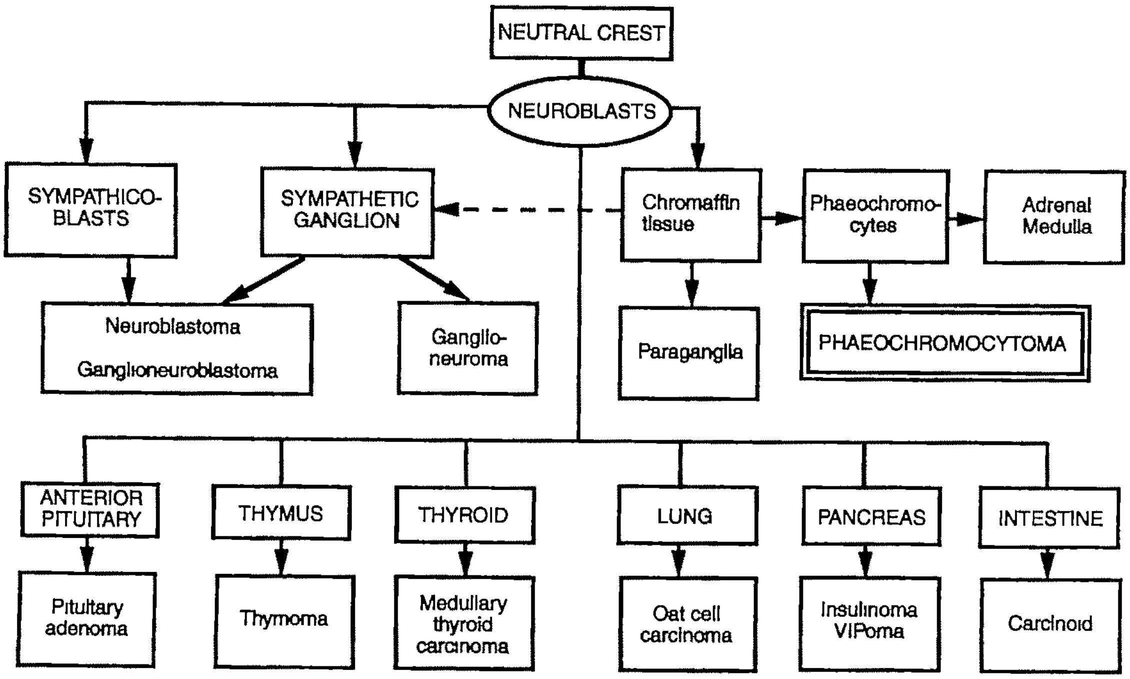


Fig 1 Classification of tissues and associated tumours derived from ectodermal cells of the neural crest[6 71]

anterior pituitary, but phaeochromocytoma is not a feature in this syndrome.

MEN 2

MEN 2 is an autosomal dominant syndrome with high penetrance and varying expression. Three sub-types are now recognized: MEN 2A, B and C. In MEN 2A (Sipple's syndrome),[85] medullary thyroid carcinoma is associated with phaeochromocytoma (in about half the patients) and hyperparathyroidism. Phaeochromocytomas in this syndrome are frequently bilateral, although sometimes the tumour is unilateral and the other adrenal is diffusely enlarged and nodular. The medullary thyroid carcinoma is diagnosed by immunocytochemical staining for calcitonin in needle biopsies, and the diagnosis is usually made earlier than that of phaeochromocytoma, whether linked or sporadic. Patients who have been treated for medullary thyroid carcinoma should be screened for phaeochromocytoma. Urinary screening reveals a higher incidence of epinephrine-secreting tumours in MEN 2A by comparison with sporadic phaeochromocytoma. Genetic screening for medullary thyroid carcinoma has been used to identify children at risk of developing the MEN syndrome, and I have anaesthetized two such children, aged 10 and 12 yr, for prophylactic thyroidectomy. These children will require regular screening to detect the probable future development of phaeochromocytoma. In MEN 2B there is medullary thyroid carcinoma, phaeochromocytoma and a specific phenotype consisting of a Marfan-like body habitus, mucosal neuromas and intestinal ganglioneuromas.[27 50] Parathyroid involvement is very uncommon in this syndrome. Phaeochromocytomas are generally a late manifestation in this syndrome, and are rarely bilateral or malignant. This subtype, which has previously been classified as MEN 3,[50] accounts for about 5% of all MEN 2. MEN 2C consists of patients having familial inherited medullary thyroid carcinoma without any other endocrine manifestation.[61]

It seems probable that *RET* gene mutations occur in thyroid parafollicular C cells, adrenal chromaffin cells and autonomic and intestinal paraganglia, causing the neoplastic changes in these syndromes.

Von Recklinghausen disease (neurofibromatosis)

Type 1 neurofibromatosis (NF1) is a rare (one in 3000) autosomal dominant disorder produced by somatic mutations in the *NF1* gene on chromosome 17, but only 1% of patients with this condition develop phaeochromocytoma.[61] The clinical association of *café-au-lait* spots and neurofibromata should raise a suspicion of a phaeochromocytoma.

Von Hippel–Lindau syndrome

This rare and complex syndrome includes retinal angiomatosis (von Hippel disease), cerebellar haemangioblastoma (Lindau disease), pancreatic cysts, renal cysts and carcinoma and epididymal cystadenoma. The adrenal glands may be involved, with an associated phaeochromocytoma.[11]

Clinical presentation

Hypertension is one of the commonest clinical conditions with which patients present to their general practitioner. Hypertension is the commonest presenting sign in patients with phaeochromocytoma. However, only one in 400–800 hypertensive patients has a phaeochromocytoma. Most general practitioners and, indeed, most physicians do not think 'phaeochromocytoma' when they encounter a new hypertensive patient in their practice or clinic. A substantial proportion of phaeochromocytomas secrete predominantly norepinephrine, often in huge quantities, sometimes paroxysmally, but usually sustained; thus sustained hypertension is the commonest presentation for this tumour.[57] Headache, the commonest symptom secondary to hypertension, is unlikely to alert the attending physician to the possibility of such a rare tumour. However, when the headaches are intermittent but regular, severe and associated with nausea and vomiting, or with slow palpitations (baroreceptor-induced bradycardia), the inconceivable possibility should cross the physician's mind. In my (recently published) series,[77] 85% of patients first presented with hypertension, subsequently linked with markedly increased urinary norepinephrine secretion. Prolonged exposure of the circulation to high circulating norepinephrine concentrations results in constriction of both arteriolar and venous segments with a marked decrease in circulating blood volume. Such events used to be more common when phaeochromocytoma was less frequently diagnosed and treated. However, patients with unrecognized phaeochromocytoma may be anaesthetized for other types of surgery; under these circumstances, induction of anaesthesia may cause widespread venodilation and thus cause profound arterial hypotension. Some patients present with increased blood glucose concentrations as a result of glycogenolysis together with impaired insulin release by the islet cells of the pancreas.[34 37] The overall picture depends on the relative proportions of norepinephrine and epinephrine secreted by individual tumours. Persistent, untreated hypertension in patients with norepinephrine-secreting tumours may result in left ventricular failure with systemic arterial shutdown, leading to severe metabolic acidosis and death.[37 44]

Only a small proportion, about 10–17%, of patients with phaeochromocytoma present with paroxysmal symptoms which reflect excessive secretion of epinephrine and dopamine—paroxysmal tachycardia sensed by the patient as palpitations, trembling, sweating and blanching, associated with feelings of panic and doom. The role of circulating epinephrine in the genesis of these symptoms was established as long ago as 1936;[5 68] the role of circulating dopamine is not established, though it is likely that symptoms relating to vasodilation in the gastrointestinal tract, such as nausea and vomiting, can be explained by high dopamine concentrations. The relevance of dopamine secretion in malignant and aberrant phaeochromocytomas was hinted at more recently.[1 3] Increased dopamine secretion by a malignant phaeochromocytoma has been described as a cause of increased outlet resistance of the prostatic urethra.[1] When symptoms of palpitations, sweating and fainting, accompanied by hypertension, occur after voiding urine, a phaeochromocytoma of the urinary bladder should be considered.[94 95] They account for 0.06% of all bladder tumours. Although it has been possible to measure free dopamine concentration in both blood and urine for >20 yr, few clinical biochemical laboratories routinely report dopamine excretion in 24 h urine collections. Excessive epinephrine secretion also causes hypermetabolism with weight loss, and stimulation of insulin release through a β_2-adrenoceptor mechanism,[34] although the latter may be offset by the effects of circulating norepinephrine.

Prolonged exposure to increased concentrations of circulating catecholamine may result in a form of dilated cardiomyopathy linked with ventricular failure in about one-third of patients[37 39] though it is not clear whether this results from α- or β-adrenoceptor activation. The histological picture is of myofibrillar degeneration with interstitial infiltration by mononucleocytes, with secondary fibrosis and calcification. A similar catecholamine-induced cardiomyopathy has been described in patients with prolonged sympathetic overactivity in tetanus. By contrast, hypertrophic cardiomyopathy may result from norepinephrine-induced hypertension.[82]

Phaeochromocytoma is a great mimic and may present in a huge variety of ways. Darby and Prys-Roberts[17] described a patient who presented in high-output left ventricular failure resulting from arterio–venous shunting through a huge suprarenal mass which turned out to be a phaeochromocytoma. High output failure has also been described as a complication of excessive epinephrine production with cardiomyopathy,[77] and one can only wonder whether excessive dopamine excretion could have been a contributory cause. Acute pulmonary oedema may complicate phaeochromocytoma at any time; it has been described as arising during recovery from anaesthesia[23] and as a response to a small therapeutic dose of propranolol.[77]

Phaeochromocytoma can present during pregnancy and mimic the usual symptoms and signs of toxaemia, either as simple hypertension or fulminant eclampsia. Management of anaesthesia and surgery during pregnancy follows the same principles as for the general population.[31 36 46 93] Previously undiagnosed phaeochromocytoma has been reported as complicating Caesarean section.

Phaeochromocytoma is an extremely rare tumour in children[73 91] but should be searched for in those presenting with episodic hypertension, and in the children of families with known histories of medullary thyroid cancer or phaeochromocytoma or both. Pre- and intra-operative management should follow the same principles as for adults.

Diagnosis

Once the combination of symptoms and signs has suggested a diagnosis of phaeochromocytoma, the best confirmatory test is to measure free catecholamines in a 24 h urine collection. High performance liquid chromatography with electrochemical detection allows accurate measurement of

Table 1 Normal values for catecholamines and their metabolites in plasma and 24 h urine collection

	Molecular weight	1 mg=x mol^{-6}	Plasma concentration (pg ml^{-1})	Urine concentration (nmol 24 h^{-1})
Epinephrine	183	5.46	40–100	<140
Norepinephrine	169	5.92	200–400	<800
Dopamine	152	6.58	<1400	
Metanephrine	197	5.08	<2000	
Normetanephrine	183	5.46	<5000	

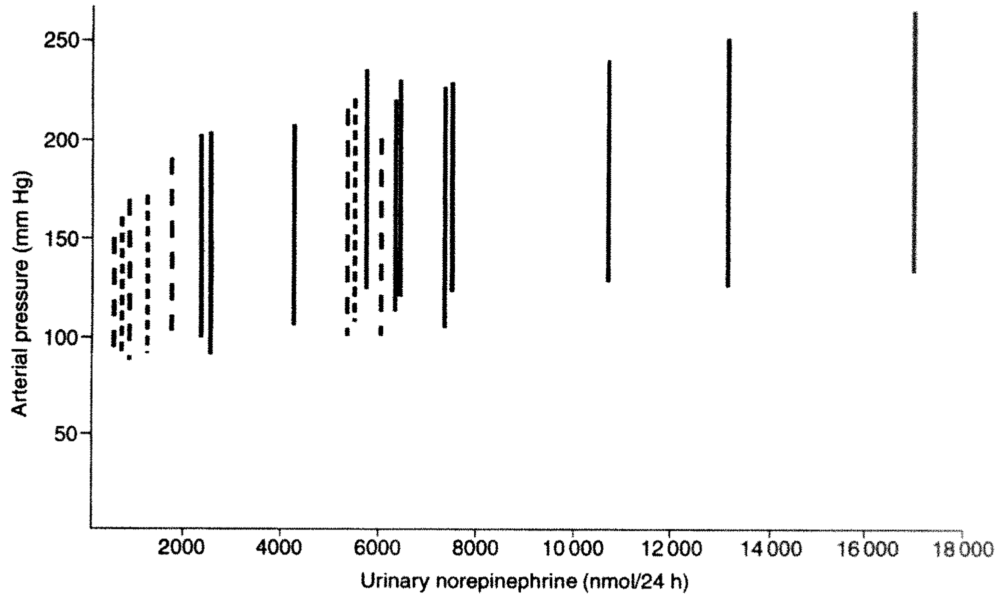


Fig 2 Relationship between systolic and diastolic arterial pressures at time of diagnosis of phaeochromocytoma and 24 h urinary norepinephrine excretion. Dashed lines indicate patients with predominantly epinephrine-secreting tumours; continuous lines indicate patients with predominantly norepinephrine-secreting tumours. Based on data from Prys-Roberts and Farndon.[77]

free epinephrine, norepinephrine and dopamine in body fluids, such as urine or blood.[47] This technique has fully superseded the older techniques for measuring urinary catecholamine metabolites, such as metanephrine or normetanephrine and their further co-metabolite vanillyl mandelic acid (VMA), sometimes referred to as hydroxy-methoxyphenyl glycol (HMPG). Dopamine is metabolized to homovanillic acid (HVA) sometimes confused with VMA. However, Eisenhofer and Lenders continue to extol the diagnostic virtues of plasma or urinary metanephrines as markers of phaeochromocytoma.[20] [21] Table 1 shows the normal values for the three endogenous catecholamines, with indications of the equivalent values for metanephrines and VMA.

Manger and Gifford[57] state that no close correlation exists between arterial pressure and plasma catecholamine concentrations. That may well be the case if one considers all phaeochromocytomas, both epinephrine and norepinephrine secretors. However, in my series of 19 patients in whom measurements of free urinary catecholamines were made, 16 patients showed predominant norepinephrine secretion of whom 13 had normal epinephrine concentrations, and a further three had slightly increased epinephrine secretion.[77] Only three patients showed predominantly elevated epinephrine secretion which was consistent with their pre-diagnosis symptoms. Five patients also showed markedly elevated dopamine secretion, the highest levels being in the three patients who showed predominantly epinephrine secretion. In those patients who had a predominant norepinephrine secretion there was a correlation between systolic and diastolic arterial pressure and the 24 h urinary norepinephrine secretion (Fig. 2). The major unknown factor is the role of dopamine in the causation of symptoms in patients with phaeochromocytoma. In my series, excessive dopamine secretion was present in five patients.[77] Such a low proportion of patients secreting epinephrine may disallow the concept that if epinephrine is the predominant catecholamine then the location of the tumour is likely to be adrenal or the organ of Zuckerkandl.

Plasma concentrations of catecholamines may give good correlations with urinary catecholamine or metabolite concentrations in patients with sustained rather than

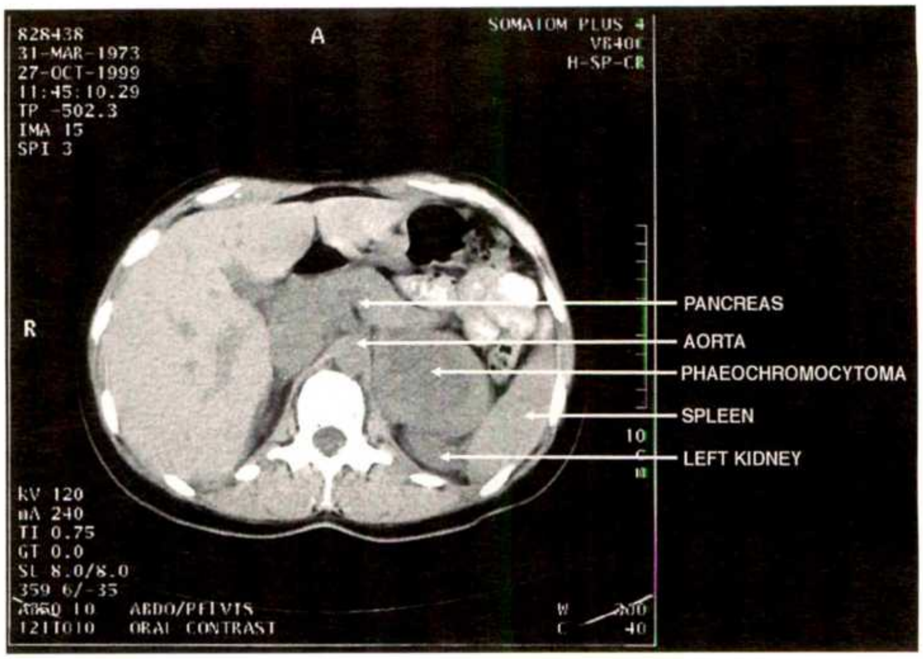


Fig 3 MRI scan of a patient with a moderately large left-sided phaeochromocytoma.

episodic symptoms. Measurements of plasma catecholamine concentrations made during an episode of cardiovascular instability may exaggerate the nature of the phaeochromocytoma.

Localization

Once the diagnosis of phaeochromocytoma has been confirmed by elevated urinary catecholamines, it is essential to start the process of localization. Shortly after Hull's review,[37] magnetic resonance imaging (MRI) was introduced and rapidly acquired a reputation for being pre-eminent as a method for identifying phaeochromocytoma.[24] Over the past 10 yr, it has become apparent that MRI (Fig. 3) and computerized tomography (CT) both provide accurate and consistent identification of the majority of phaeochromocytomas, particularly when the tumours occur in the suprarenal area.[41] Tumours as small as 1 cm can be recognized. Cystic phaeochromocytoma may be particularly easy to diagnose by MRI because such tumours have a high water content and so give a good signal.

Recurrent tumours, metastases and tumours in unusual sites may have to be identified with the radiopharmaceutical agent [^{131}I]*meta*-iodobenzyl guanidine (MIBG).[92 103] MIBG has been effective in identifying uncommon sites such as the urinary bladder and the pericardium,[80] but has some disadvantages in that it may be taken up by neuroblastomas, medullary thyroid carcinomas, carcinoids and small-cell carcinomas of the lung. Drugs such as labetalol,[49] reserpine, adrenergic neurone blockers, calcium channel blockers and some tricyclic antidepressants are known to interfere with the uptake of MIBG.

Older techniques, such as the pentolinium[10] and clonidine suppression test,[7 48] glucagon provocative test[7] and selective adrenal vein blood sampling, are now rarely needed.

Preoperative pharmacological control

Once the diagnosis of phaeochromocytoma has been made, there is little doubt that surgery is the only curative procedure, but immediate pharmacological control of the adverse effects of circulating catecholamines is essential. Immediate surgery is rarely essential; the main objective is to control arterial pressure, heart rate and arrhythmias and, especially, to allow blood volume to be restored to normal.

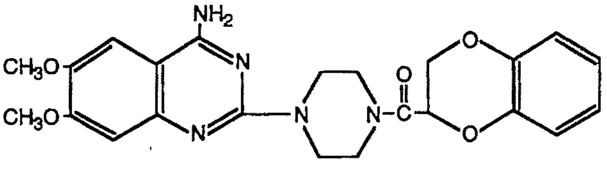
α-Adrenoceptor antagonists

Phenoxybenzamine has been widely used since the early 1950s[40] as the mainstay of pre- and perioperative control of blood pressure in patients with phaeochromocytoma,[37 57 88] and was still being advocated recently.[9 26 55 78] Advantages claimed for phenoxybenzamine are that it has a long duration of action, allowing twice-daily oral ingestion, and that it produces non-competitive blockade as a result of covalent binding of the drug to the receptor.[35] The latter effect is claimed to prevent the effects of surges of catecholamine release during the preoperative preparatory period.[9 37]

Disadvantages of phenoxybenzamine are numerous. First, being a non-selective α-adrenoceptor antagonist, it blocks α_2-adrenoceptors, especially those on the presynaptic membrane of adrenergic neurone terminals which are part of a negative feedback loop regulating release of norepinephrine.[51] Consequently, the release of norepinephrine at cardiac sympathetic nerve endings is uninhibited and what would otherwise be normal sympathetic nerve activity causes undesirable chronotropic and inotropic effects. Traditionally, these have been controlled by adjuvant β-adrenoceptor antagonists.[37] [57] Second, the non-competitive covalent binding results in an irreversible block which has been attributed to alkylation of the α-receptor by a highly reactive carbonium ion formed by cleavage of the tertiary amine of phenoxybenzamine.[35] Although the pharmacological half-life of phenoxybenzamine is about 24 h, the prolongation of the receptor blockade depends on the rate of re-synthesis of the receptors.[32] [33] One of the main findings of my recent study was the marked prolongation of α-adrenoceptor blockade in the postoperative period despite stopping the administration of phenoxybenzamine 24–48 h before the operation.[77] A number of postoperative problems can be attributed to such an effect. Patients who have been subjected to long-term phenoxybenzamine therapy are often very somnolent in the first 48 h after surgery,[37] and this may result from persistent central α_2-adrenoceptor blockade. As the systemic arterioles are insensitive to α-adrenoceptor agonists in such patients, it has been established practice to expand the intravascular volume in excess of predicted or measured fluid losses,[37] resulting in marked interstitial fluid retention and widespread peripheral oedema. Other disadvantages of phenoxybenzamine given before an operation are that it causes somnolence, headache and a stuffy nose—all central side-effects related to α_2-adrenoceptor blockade—and consistent and marked postural hypotension. The latter occurred in all eight of the phenoxybenzamine-treated patients in my series.[77]

Phenoxybenzamine should be started in small doses (10 mg, two or three times daily) and increased gradually until either all signs of pressor activity have been suppressed, or until the patient complains of the side-effects of postural hypotension or a stuffy nose, or both, usually when doses exceed 90 mg day^{-1}. Tachycardia should be controlled by the careful introduction of a β-adrenoceptor antagonist. In my series,[77] physicians chose a variety of β-adrenoceptor antagonists (propranolol 160 mg bd, atenolol 100 mg od, metoprolol 150 mg × 3, labetalol 100 mg bd).

Selective competitive α_1-adrenoceptor blockade with prazosin in patients with phaeochromocytoma was advocated by Wallace and Gill[100] and others in the Americas,[15] [70] but failed to achieve widespread popularity. One reason for this may be that physicians were reticent to use greater doses of prazosin, then a new drug in the treatment of hypertension, to control patients' arterial pressure. Prazosin, a drug with high first-pass metabolism,[98] was therefore probably given in inadequate dosage, even though by sparing α_2-adrenoceptors, it would have minimized β-adrenergic activation in the heart.[28] Because of its high clearance (4–5 ml min^{-1} kg^{-1}) and its short elimination half-life (2–3 h), prazosin blood concentrations may decrease to ineffective levels at the time of surgery if the last dose was given on the previous night. Russell and colleagues[78] claim that phenoxybenzamine pretreatment provided superior intraoperative stability to prazosin, though this was a comparison of only one patient receiving prazosin (no dosage given) with 12 patients receiving phenoxybenzamine. The hypotensive effect of prazosin is concentration dependent and this drug may also have a profound hypotensive effect on the first dose. This latter effect may reflect the immediate effects of arteriolar dilation in a patient who has been in a state of venoconstriction and arteriolar constriction with low circulating blood volume,[38] a state characteristic of prolonged elevated norepinephrine secretion. Prazosin should be introduced in a dose of 1 mg every 8 h and gradually increased up to 12 mg daily.[37]



Doxazosin

Fig 4 Structure of doxazosin, a selective α_1-adrenoceptor antagonist with a bioavailability of >70%, a low plasma clearance and a long elimination half-life. Doses of 2–16 mg day^{-1} can maintain effective α_1-adrenoceptor blockade over a 24 h period

Doxazosin (Fig. 4) is a competitive and selective α_1-adrenoceptor agonist which, being non-lipophilic, has a high bioavailability (70%) and does not readily cross the blood–brain barrier, and has a long duration of action allowing once-a-day dosing.[4] [13] [22] Mean peak plasma concentrations of about 8 μg litre^{-1} can be achieved within 4 h of a single oral dose of doxazosin 1 mg, and increase linearly with doses up to 16 mg daily.[14] Doxazosin increases renal perfusion, decreases renal vascular resistance and does not modify the renal response to exercise.[18] [86] [104] I selected doxazosin in 1991 as a drug with a near-ideal profile for the preoperative management of patients with phaeochromocytoma. Since then 20 patients, 18 with phaeochromocytoma and two with paraganglionoma, have been treated successfully with doxazosin in doses from 2 to 8 mg day^{-1}.[77] Doxazosin was used alone in 11 of these patients, all of whom had been diagnosed as predominantly norepinephrine secretors based on urinary free catecholamine measurements. Five patients also received small doses of β-adrenoceptor antagonists because the primary physicians could not be persuaded to omit the drug! Only one patient complained of moderate postural hypotension. Preoperative control of arterial pressure was at least as good as that achieved with phenoxybenzamine (Table 2). As doxazosin does not block the presynaptic α_2-adrenoceptors which regulate norepinephrine release at cardiac adrenergic nerve endings, it is unnecessary to administer β-adrenoceptor antagonists unless the patient has an epinephrine-secreting tumour. Three patients with predominantly epinephrine- (and dopamine-) secreting tumours were treated effectively

Table 2 Preoperative blood pressures in patients treated with phenoxybenzamine or doxazosin.[15] Data are expressed as mean (SD)

	Phenoxybenzamine (n=8)	**Doxazosin (n=18)**	***P***
Pre-operative arterial pressure (mm Hg)			
systolic	162 (17.7)	150 (23.9)	0.220
diastolic	92 (15.3)	77 (15.5)	0.029
Heart rate (beats min^{-1})	71 (12.6)	75 (11.1)	0.451

with a combination of doxazosin (2–4 mg day^{-1}) and labetalol (200–400 mg day^{-1}).

While doxazosin controls arterial pressure satisfactorily in the preoperative management of the patient, there will still be a need for supplementary α- and β-receptor block during surgical manipulation of the tumour. In my series there was no significant difference in intraoperative phentolamine or labetalol requirements between the phenoxybenzamine- and doxazosin-treated patients.[77]

Terazosin is an alternative selective α_1-adrenoceptor antagonist with pharmacokinetic characteristics similar to those of doxazosin, but with a shorter half-life.

β-Adrenoceptor antagonists

There are two reasons for using β-adrenoceptor antagonists in the preoperative treatment of patients with phaeochromocytoma. The first is to limit symptoms and signs referable to increased circulating epinephrine, mainly manifest as tachycardia with or without cardiac arrhythmias. These will be evident in patients with predominantly epinephrine- (and dopamine-) secreting tumours. As the prime objective is to limit excessive tachycardia with or without arrhythmias mediated through β_1-adrenoceptors, it is logical to use selective β_1-adrenoceptor antagonists such as atenolol (100 mg day^{-1}) or bisoprolol (10–20 mg day^{-1}) in order to minimize undesirable side-effects in the bronchi or peripheral vasculature. Labetalol (100–400 mg day^{-1}) has been chosen because it antagonizes both α- and β-adrenoceptors. The α-adrenoceptor block is competitive but weak, but will supplement additively any pre-existing α-block resulting from the use of phenoxybenzamine, prazosin or doxazosin. Carvedilol (12.5–50 mg day^{-1}) is another β-adrenoceptor antagonist having weak α-blocking effects.[8] Other non-selective (i.e. mixed β_1 and β_2) antagonists such as propranolol (40–240 mg day^{-1}) or metoprolol (50–200 mg day^{-1}) may be used, but care must be exercised in preselecting patients who do not have a history of obstructive airway disease or peripheral arterial disease. Celiprolol (200–400 mg day^{-1}), which has β_1 antagonist and β_2 agonist effects,[59] may be the drug of choice in such patients.

The second reason is to block excessive cardiac sympathetic drive secondary to suppression of the presynaptic α_2-regulating mechanism by drugs such as phenoxybenzamine. In my series [77] it has been found to be unnecessary to use β-adrenoceptor antagonists with doxazosin, except in patients known to be epinephrine secretors.

Suppression of β-adrenoceptor-mediated cardiac sympathetic activity in the absence of adequate arteriolar dilation may precipitate acute pulmonary oedema.[37] A 17 yr old female in my series[77] went into acute pulmonary oedema shortly after a small intravenous dose of propranolol to control tachycardia after admission to hospital. It is therefore considered to be very unwise to administer β-adrenoceptor antagonists to patients with phaeochromocytoma without first ensuring adequate arteriolar dilation,[37] and then only under continuous cardiovascular monitoring.

Other drugs

Although there are devotees of the use of other antihypertensive drugs in the preoperative management of patients with phaeochromocytoma, there is little evidence to support their use. One report described exclusive use of calcium channel blockers in the pre- and intra-operative control of 10 patients with phaeochromocytoma.[76] Another suggested that nifedipine blocked surges of sympathetic activity in one patient with phaeochromocytoma of the urinary bladder,[52] and another reported suppression of symptoms in a patient with norepinephrine-induced cardiomyopathy.[82] The advantages of ACE inhibitors (ramipril) or angiotensin II antagonists (such as losartan or irbesartan) in reversing left ventricular hypertrophy are of doubtful value in the preoperative management of most phaeochromocytomas as the hypertensive stimulus (norepinephrine) usually reverts to normal after surgery.

Alpha-methyl-*p*-tyrosine (AMPT) was used in the 1960s to inhibit the rate-limiting conversion of tyrosine to dopa by suppressing tyrosine hydroxylase,[37] thus decreasing the synthesis of catecholamines by 40–80%. Its use has not stood the test of time, probably because of the high incidence of undesirable side-effects. However, there is an interesting report of its use in a child with catecholamine-induced dilational cardiomyopathy.[39]

Management of anaesthesia and surgery

Surgery

The management of anaesthesia and monitoring for surgery of phaeochromocytoma and paraganglionomas will depend to some extent on the surgical approach. Adrenalectomy for phaeochromocytoma has traditionally been performed by open lateral retroperitoneal surgery, though a transabdominal approach may be necessary in a few patients. Recently, laparoscopic transperitoneal excision of phaeochromocytoma has become feasible. Open surgery is usually quicker, but the patient may require longer postoperative hospitalization. In the absence of complications resulting from persistent adrenergic blockade, patients may be ready to leave hospital 36–48 h after laparoscopic surgery.

Manipulation of the tumour during open surgery, with its haemodynamic responses, may be inevitable but can usually be of short duration. In my experience, laparoscopic excision of a phaeochromocytoma requires persistent tissue traction and diathermy or ultrasound coagulation which may cause sustained haemodynamic consequences of at least the same severity as may be expected during open surgery, but for a rather longer period of time. The *quid pro quo* is the shorter postoperative hospital stay. Laparoscopic surgery may prove too difficult, requiring open surgery on the same occasion or subsequently. The surgical approach will also influence the anaesthetist's plan for postoperative analgesia.

Anaesthesia

To quote Hull,[37] 'Since the first successful operation by the Swiss surgeon Roux in 1926, almost every possible anaesthetic technique has been advocated.' I share Hull's view that a rational anaesthetic technique should be based on sound pharmacological principles rather than an 'idiosyncratic fondness for particular drugs or methods'! I differ from Hull only in preferring a combined regional and general anaesthetic technique, using a segmental mid- to low-thoracic epidural combined with adequate general anaesthesia, and selective adrenergic antagonists, phentolamine and labetalol to control haemodynamic surges in response to tumour manipulation. Schüttler has also advocated rational management during surgery based on measurement of catecholamine secretions.[81]

A practical rational technique

The following basic technique, with minor changes over a period of 32 yr, has been uniformly successful in >50 operations for phaeochromocytoma, in Oxford and Bristol. I changed from halothane to isoflurane when the latter became available in the early 1980s and substituted atracurium for alcuronium at about the same time. Apart from one patient who died of an inoperable malignant phaeochromocytoma within a week of attempted surgery, there have been no other deaths within 31 days of surgery, and no serious postoperative complications. In the earlier patients in my series, refractory hypotension in the early postoperative period can, with hindsight, be attributed to the undesirable lingering effects of phenoxybenzamine therapy (see below). Since the change to preoperative management with doxazosin in 1992, the subsequent 21 patients have been remarkably free of intra- or post-operative problems.

The last preoperative doses of adrenergic antagonists should be given at about 22.00 h on the evening before surgery, anticipating a start of anaesthesia at 08.30 h. Phenoxybenzamine, if it has been used preoperatively, should be withdrawn at least 48 h before surgery. Such a plan results in a patient whose relevant adrenoceptors are adequately blocked (see below), and whose haemodynamic state is stable up to the time of surgical manipulation of the tumour. Oral premedication with temazepam (10–30 mg) suffices in most patients.

Peripheral venous, arterial and central venous (antecubital or internal jugular vein entry) catheters are placed under local anaesthesia and haemodynamic monitoring is established together with ECG (CM5 lead) and pulse oximeter. I have only once felt the need for balloon-occluded pulmonary artery pressure measurement.[17]

After preoxygenation, I induce anaesthesia with fentanyl 5 $\mu g\ kg^{-1}$ and propofol 1 $mg\ kg^{-1}$ followed by atracurium 0.5 $mg\ kg^{-1}$ when the patient no longer responds to command. Following tracheal intubation and insertion of a nasogastric tube, the patient's lungs are ventilated with a tidal volume of 10 $ml\ kg^{-1}$ at a rate of 10–12 breaths min^{-1}, using a circle system, either without a soda–lime absorber, or with a soda–lime absorber with a partial bypass. This allows controlled partial rebreathing of carbon dioxide, allowing the patient's end-tidal P_{CO_2} to be controlled at 38 mm Hg (5.1 kPa). I maintain anaesthesia with isoflurane in an air–oxygen mixture to achieve an $F_{I_{O_2}}$ of about 0.5, and an end-tidal isoflurane concentration of about 0.9%. The patient can then be turned, carefully, on to their side for sterile placement of an epidural catheter at an appropriate site for the proposed surgical incision, usually a paraspinous mid- (T9–10) to low- (T12–L1) thoracic Tuohy needle placement, allowing a catheter length of 5 cm in the epidural space. I inject bupivacaine (4 ml of 0.5% solution) into the epidural space before placement of the catheter and I give further incremental doses of 4 ml of 0.5% bupivacaine at 1 h intervals throughout surgery. I have never seen a severe hypertensive or tachycardic response to turning the patient. The patient is then transferred to the operating theatre and positioned for the planned surgical approach. This technique is equally applicable for both open and laparoscopic surgical approaches. For laparoscopic surgery, the patient is placed in the full lateral position with the anticipated tumour site uppermost.

Once the epidural block is effective, further doses of fentanyl or neuromuscular blocking drug are rarely required for open surgery, although during laparoscopic surgery it may be necessary to use small doses of either drug to suppress the drive to breathe as carbon dioxide is absorbed from the peritoneal cavity.

Pharmacological control of catecholamine release during surgery

The combination of adequate regional anaesthesia with general anaesthesia sufficient to prevent the patient coughing on the tracheal tube provides satisfactory conditions for the initial surgical incision and exposure of the tumour. Manipulation of the tumour, however gently performed, usually causes a brisk haemodynamic response. In patients with norepinephrine-secreting tumours this response is predominantly a pressor response, the systolic arterial pressure rising from a basal 100–120 mm Hg about 20 s

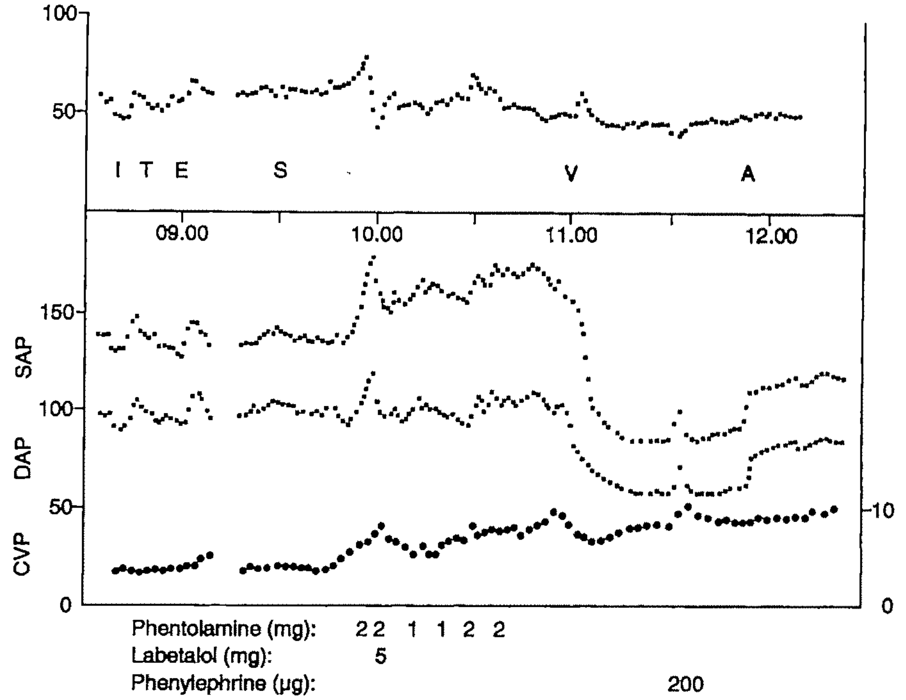


Fig 5 Computer reconstruction of patient record (Hewlett-Packard Merlin) for patient 20,[77] a predominantly norepinephrine secretor (7500 nmol 24 h^{-1}), showing changes of heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressures, and central venous pressure (CVP) Note the response to direct tumour handling at 09.50 h, in which systolic and diastolic arterial pressure increase swiftly together with an initial increase in heart rate. When the systolic arterial pressure reaches 160 mm Hg, there is a sudden reversal of the heart rate response, presumably as a result of a baroreflex response; this occurs before the phentolamine and labetalol have reached their relevant receptors. This biphasic response was observed in four other patients all of whom had predominantly norepinephrine-secreting tumours Note also the sudden exponential decrease in arterial pressure immediately after the final vein draining the tumour had been ligated. This response was observed in all the patients having predominantly norepinephrine-secreting tumours. Note the diminished arterial pressure increase (approximately 16 mm Hg) in response to phenylephrine 200 µg, indicating a substantial degree of α-adrenoceptor blockade. Note also the step increase in arterial pressure when the patient recovers consciousness Key: I=induction, T=tracheal intubation, E=turning the patient on to side to perform epidural, S=initial surgical incision, V=ligation of final connecting vein, A=patient awake and responding to command

Table 3 Supplemental doses of phentolamine and labetalol required in patients pretreated with phenoxybenzamine or doxazosin[77]

Dose (mg)	Phenoxybenzamine (n=8)	Doxazosin (n=18)	P
Phentolamine	9.6 (6.8)	11.1 (7.6)	0.652
Labetalol	33.1 (8.4)	15.8 (8.2)	0.080

after surgical manipulation. I attempt to give phentolamine 2 mg i.v. in anticipation of this event, partly to suppress it, and partly to assess the patient's response to such a dose. In the event that this pressor response is accompanied by tachycardia, I use 5 mg incremental doses of labetalol to suppress it (Fig. 5). Subsequently it is possible to control the surges of systolic arterial pressure and heart rate by judiciously timed combination of these two drugs, together with transient increased concentrations of isoflurane. The average phentolamine and labetalol requirements in my recent series[77] are shown in Table 3. In patients with a predicted predominant epinephrine (and dopamine) secretion I would anticipate an increase in heart rate by giving labetalol 20 mg i.v. over a period of 10 min before anticipated tumour handling, followed by phentolamine or labetalol, or both, to control anticipated or extant surges (Fig. 6). Esmolol, having an ultra-short elimination half-life, has been proposed as a suitable drug for the control of β-adrenoceptor-mediated haemodynamic changes.[69 79 105] There is little evidence that residual β-adrenoceptor blockade by longer-acting drugs is a drawback.

In most patients with a unilateral phaeochromocytoma it is possible to identify the moment the surgeon ligates the predominant or last major emptying vein from the tumour as an exponential decrease of arterial pressure over a 5 min period to a level below the pre-handling arterial pressure (Fig. 5).

In patients pretreated with phenoxybenzamine it has been my experience that mean (SD) systolic arterial pressure remains relatively low (100 (12) mm Hg) during the first 1–2 h after surgery despite vigorous attempts to fill the circulation with colloid solutions (previously dextran 70, now gelatin) to increase the central venous pressure to ≥8 mm Hg. Such patients can be unresponsive to huge doses of α_1-adrenoceptor agonists such as phenylephrine, methox-

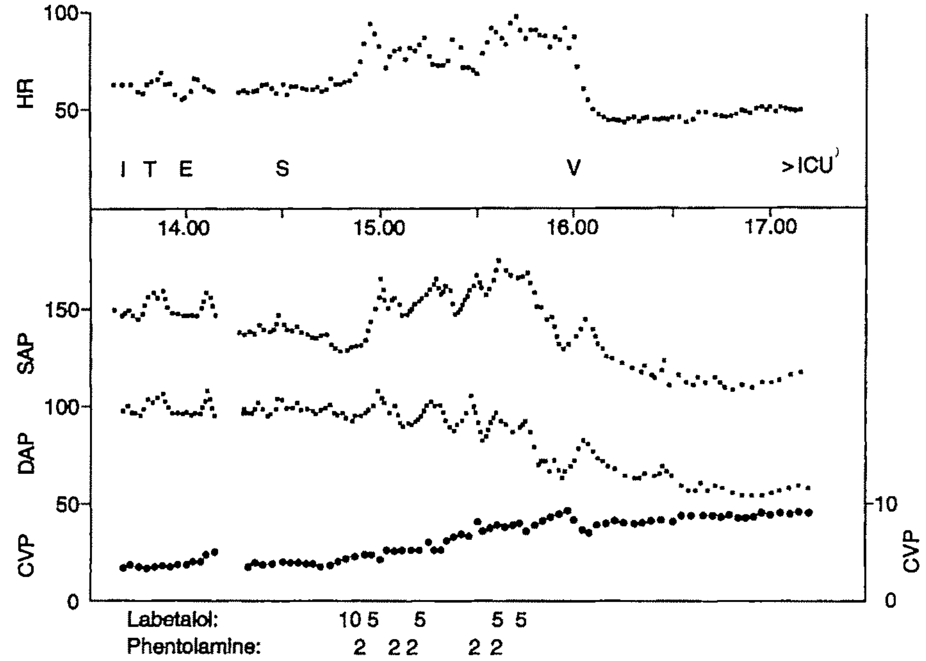


Fig 6 Computer reconstruction of patient record (Hewlett-Packard Merlin) for patient 17,[77] showing changes of heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressures and central venous pressure (CVP). This patient had a predominantly epinephrine- (1571 nmol 24 h^{-1}) and dopamine- (14 916 nmol 24 h^{-1}) secreting tumour. Note the tachycardia in response to initial tumour handling despite labetalol 10 mg given 5 min earlier, and the exponential decrease of heart rate to <50 beats min^{-1} after ligation of the final draining vein of the tumour. Key as in Fig. 5.

amine or norepinephrine (see below). Patients pretreated with doxazosin are much less refractory, indeed their systolic arterial pressure remains moderately low during the remainder of the surgical procedure but returns sharply to normal levels (118 (14) mm Hg) as soon as consciousness returns and cerebral arousal stimulates the sympathetic nervous system.[77] Such patients require much less fluid loading in the postoperative period and consequently have a significantly lower positive fluid balance in the first three postoperative days (2800 (1380) ml) compared with patients receiving phenoxybenzamine (4800 (2474) ml).[77] Most patients (93%) pretreated with phenoxybenzamine were clinically oedematous during this period, whereas only one of the 19 patients who received doxazosin was oedematous.

All patients have been returned, breathing spontaneously and with full analgesia, to a high-dependency bed in the intensive care unit (ICU) for monitoring and observation, and most have been discharged to the general ward the following day.

Assessment of adrenergic block

Since 1988, I have assessed the degree of α-adrenoceptor blockade in all patients with phaeochromocytoma.[77] This was done by constructing dose–response curves representing the increase in systolic arterial pressure to increasing intravenous doses of phenylephrine.[72] These curves were constructed before induction of anaesthesia in the awake patient in the anaesthetic room, during surgery before tumour handling, at the end of surgery before departing to the ICU and on the first and sometimes later postoperative days. These dose–response curves were an extension of a method which was validated for β-adrenoceptor antagonists.[16] Patients pretreated with β-adrenoceptor antagonists were tested in the same manner, deriving dose–response curves for isoprenaline.

Thus patients treated with varying doses of adrenoceptor antagonists can be assessed before, during and after surgery, to enable the anaesthetist to control the patient's state of protection more precisely. The data obtained from patients receiving phenoxybenzamine established the extensive duration of non-competitive α-blockade,[77] up to 2 weeks after the drug has been discontinued; confirming previous evidence from studies in animals.[32] [33] The data from patients receiving doxazosin confirm the competitive nature of the antagonism in patients with phaeochromocytoma and the very rapid return to normal within 24–36 h after discontinuing the doxazosin.[77]

Alternative anaesthetic and adrenoceptor antagonist strategies

Hull, in his 1986 review, preferred a balanced anaesthetic scheme of enflurane in nitrous oxide supplemented with an alfentanil infusion and sustained neuromuscular block.[37] This technique was supplemented by intravenous infusion of a potent vasodilator to control hypertension, and a β-adrenoceptor antagonist. In his review, Hull did not indicate specifically his choice of arteriolar dilator, but indicated that sodium nitroprusside (SNP) 'is currently the most widely used'. While I would question the accuracy of this statement, even at that time, there is ample evidence that SNP has been successfully used.[9 67 96] While SNP may be effective in causing arteriolar dilation and suppressing the hypertensive response to circulating catecholamines, evidence from our own studies show that isoflurane is as effective as an arteriolar dilator and almost as rapid in onset, while avoiding the undesirable metabolic consequences of prolonged SNP infusions.[62 63] SNP was specifically advocated to supplement the 'anaesthetic' management (fentanyl 50 μg kg^{-1} alone) of an 11 yr old child with a single ventricle and phaeochromocytoma to avoid impairment of ventricular function.[96]

The most widely quoted alternative to SNP is phentolamine, a competitive α_1- and weak α_2-adrenoceptor antagonist, which can be given intravenously as an infusion or as incremental doses of 1–2 mg. Hull claims that 'phentolamine is less satisfactory because tachycardia is an invariable problem'.[37] I find this somewhat puzzling in that I have used phentolamine for all my phaeochromocytomas except two over the past 32 yr without observing a substantial tachycardia that could be attributed directly to phentolamine in any patient. Admittedly, most of my patients have also received a β-adrenoceptor antagonist during surgery and would therefore be unlikely to manifest such a tachycardia secondary to catecholamine release at cardiac nerve endings, but those are the very circumstances under which phentolamine should be used in the management of these patients.

Calcium channel blockers have been used by a number of authors, based on the concept that calcium ion transfer is essential for the release of catecholamines from the chromaffin cells of the adrenal medulla[19 54] and from adrenergic nerve endings.[99] A French group has advocated the use of calcium channel blockers exclusively in the preoperative preparation of patients[76] and there are a number of case reports in which nifedipine or nicardipine has been used.[2 52 58 64 82] By contrast, Munro and colleagues report poor pre- and intra-operative control of a patient with a malignant phaeochromocytoma.[67]

Takahashi and colleagues[93] report the use of prostaglandin E_1[29] combined with labetalol for the preoperative management of a pregnant patient who underwent Caesarean section at 35 weeks.

Much has been made of the dangers of using drugs which potentially release histamine because of the risk of provoking catecholamine release from chromaffin granules.[37] Three drugs which have been implicated are *d*-tubocurarine, morphine and atracurium. Morphine has been used safely[30] and, although Hull questions the safety of atracurium,[37] I have used 0.5 mg kg^{-1} as an intubating dose in 36 patients with phaeochromocytoma since 1984 without any adverse consequences.

Magnesium sulphate

James and colleagues have championed the infusion of magnesium sulphate as the main alternative therapeutic strategy to adrenergic block during anaesthesia and surgery for phaeochromocytoma.[42 43] James bases his technique on the principle that magnesium ions inhibit the release of catecholamines from the normal adrenal medulla,[19 54] and from adrenergic nerve terminals.[99] James[42] describes a series of 17 patients in whom preoperative control was achieved with either phenoxybenzamine (eight patients) or prazosin (eight patients), and in whom operative control was achieved with a loading dose of magnesium sulphate (40–60 mg kg^{-1}) followed by an infusion of 1–2 g h^{-1}, designed to achieve serum magnesium concentrations between 2 and 4 mmol litre^{-1}. Good stability, defined as an arterial pressure within 30 mm Hg of the preoperative value, was achieved in 12 of the 17 patients; sodium nitroprusside was required in five patients. Supplementary doses of magnesium sulphate were required in all patients at the time of tumour manipulation. In two of the five patients in whom plasma catecholamine measurements were made during surgery, magnesium sulphate was ineffective in blocking the release of catecholamines.

Two of the patients in James' series were pregnant at the time of surgery.[43] One had inadequate control because therapeutic concentrations of magnesium were not achieved, whereas the other, who also underwent Caesarean section, was well controlled.

Magnesium sulphate 2 g h^{-1} has also been used successfully in combination with epidural blockade in a patient with bilateral phaeochromocytoma complicating severe coronary artery disease.[75]

Whether the use of magnesium sulphate results in better outcomes than the use of phentolamine or sodium nitroprusside can be determined only by a properly designed randomized trial in which many variables, such as type of catecholamine-secreting tumour or preoperative drug therapy, have been controlled. In view of the rarity of the condition, such trials are unlikely to be undertaken, and in the final analysis anaesthetists will have to rely on their 'idiosyncratic fondness for particular drugs or methods'.[37] For completeness, the following anaesthetics/techniques have been reported during the past 12 yr, usually as single case reports: midazolam/sufentanil infusion,[83] midazolam/fentanyl infusion,[58] propofol/fentanyl infusion,[90] magnesium sulphate combined with glyceryl trinitrate,[31] desflurane,[53] sevoflurane with adenosine triphosphate[60] and esmolol infusion (despite the fact that the patient had a norepinephrine-secreting tumour).[79]

Postoperative management

The main postoperative complication of surgery for phaeochromocytoma is persistent arterial hypotension which may be refractory to intravascular volume replacement and adrenoceptor agonists. This is an extension of the process referred to earlier and is the result of a number of factors. While the excised tumour was active, the catecholamine output of the contralateral adrenal gland was effectively suppressed and the patient's relevant adrenoceptors were down-regulated. Thus in the absence of catecholamines from the tumour, the only source will be norepinephrine liberated from adrenergic nerve endings. This depends on generalized sympathetic nervous activity which is considerably diminished during anaesthesia as a result of the lack of 'arousal' and its effects in stimulating the hypothalamus. In the 19 patients pretreated with doxazosin in my series,[77] mean (SD) systolic arterial pressure increased by 15 (8) mm Hg following recovery of consciousness to 118 (14) mm Hg; by comparison with an increase of 8 (6) to 100 (12) mm Hg in the eight patients who had been pretreated with phenoxybenzamine. However, the latter patients received an average of 1200 ml gelofusin, whereas those who had received doxazosin received an average of 350 ml gelofusin, both based on an attempt to maintain central venous pressure at about 8 mm Hg. It is tempting, therefore, to ascribe such problems to the use of phenoxybenzamine and the persistent α-adrenoceptor blockade. However, the shift of the phenylephrine dose–response curves was comparable in the two groups of patients during the first two postoperative hours, largely as a result of the additional effects of phentolamine used during surgery.

Conclusion

Phaeochromocytoma has a way of presenting unexpectedly, frequently during surgical operations for other conditions, creating a set of potentially dangerous circumstances. Even when the patient's condition is recognized and treated pharmacologically to control responses to catecholamine release, management of anaesthesia can be highly stressful for the inexperienced anaesthetist. Developments in surgical technique, such as laparoscopic excision, may not decrease the problems of intraoperative management, although the patient may well leave hospital much sooner than after open surgery. Patients with phaeochromocytoma or paraganglionoma should ideally be managed by an experienced team of endocrinologists, endocrine surgeons and anaesthetists.

References

1 Araki S, Kato M, Kase H, Okada K. Hyperdopaminemia may produce an increased outlet resistance of the prostatic urethra: a case report of malignant pheochromocytoma. *J Urol* 1995; **153**: 1614–5

2 Arai T, Hatano Y, Ishida H, Mori K. Use of nicardipine in the anesthetic management of pheochromocytoma. *Anesth Analg* 1986; **65**: 706–8

3 Awoke S, Perlstein RS. Dopamine and norepinephrine secreting intrapericardial pheochromocytoma in a normotensive patient *South Med J* 1985; **78**: 994–8

4 Babamoto KS, Hirokawa WT. Doxazosin: a new α_1-adrenergic antagonist. *Clin Pharm* 1992; **11**: 415–27

5 Beer E, King FH, Prinzmetal M. Pheochromocytoma with demonstration of pressor (Adrenalin) substance in the blood preoperatively during hypertensive crises. *Ann Surg* 1937; **106**: 85–91

6 Bolande RP. The neurocrestopathies. a unifying concept of disease arising in neural crest maldevelopment. *Hum Pathol* 1974; **5**: 409–29

7 Bravo EL, Gifford RW Jr. Pheochromocytoma: diagnosis, localization and management. *N Engl J Med* 1984; **311**: 1298–303

8 Bristow MR, Larrabee P, Minobe W *et al.* Receptor pharmacology of carvedilol in the human heart. *J Cardiovasc Pharmacol* 1992; **19** (Suppl 1): S68–S80

9 Brown BR Jr. Anaesthesia for phaeochromocytoma In: Prys-Roberts C, Brown BR Jr, eds. *International Practice of Anaesthesia.* Oxford: Butterworth Heinemann, 1996; 1/83/1–7

10 Brown MJ, Allison DJ, Jenner DA, Lewis PJ, Dollery CT. Increased sensitivity and accuracy of phaeochromocytoma diagnosis achieved by plasma adrenaline estimations and a pentolinium suppression test. *Lancet* 1981; **i**: 174–7

11 Chapman RC, Diaz-Perez R. Pheochromocytoma associated with cerebellar hemangioblastoma. *J Am Med Assoc* 1962; **182**: 1014–7

12 Cook JE, Ulrich RW, Sample HG Jr, Fawcett NW. Peculiar familial and malignant pheochromocytomas of the organs of Zuckerkandl. *Ann Int Med* 1960; **52**: 126–33

13 Cubeddu LX. New alpha_1-adrenergic receptor antagonists for the treatment of hypertension: role of vascular alpha receptors in the control of peripheral resistance. *Am Heart J* 1988, **116**: 133–62

14 Cubeddu LX, Fuenmayor N, Caplan N, Ferry D. Clinical pharmacology of doxazosin in patients with essential hypertension. *Clin Pharmacol Ther* 1987; **41**. 439–49

15 Cubeddu LX, Zarate NA, Rosales CB, Zschaeck DW. Prazosin and propranolol in preoperative management of pheochromocytoma. *Clin Pharmacol Ther* 1982; **32**: 156–60

16 Dagnino J, Prys-Roberts C. Assessment of beta-adrenoceptor blockade during anesthesia. Use of isoproterenol dose–response curves. *Anesth Analg* 1985; **64**: 305–11

17 Darby S, Prys-Roberts C. Unusual presentation of phaeochromocytoma. Management of anaesthesia and cardiovascular monitoring. *Anaesthesia* 1976; **31**: 913–6

18 De Leeuw PW, Van Es PN, De Bos R, Birkenhäger WH. Acute renal effects of doxazosin in man. *Br J Clin Pharmacol* 1986; **21**: 41S–43S

19 Douglas WW, Rubin RP. The mechanism of catecholamine release from the adrenal medulla and the role of calcium in stimulus–secretion coupling. *J Physiol* 1963, **167**: 288–310

20 Eisenhofer G, Lenders JW. Clues to the diagnosis of pheochromocytoma from the differential tissue metabolism of catecholamines. *Adv Pharmacol* 1998; **42**: 374–7

21 Eisenhofer G, Keiser H, Friberg P, *et al.* Plasma metanephrines are markers of pheochromocytoma produced by catechol-O-methyltransferases within tumors. *J Clin Endocrinol Metab* 1998; **83**: 2175–85

22 Elliott HL, Meredith PA, Vincent J, Reid JL. Clinical pharmacological studies with doxazosin. *Br J Clin Pharmacol* 1986; **21**: 27S–31S

23 Fahmy N, Assad M, Bathijad P, Whittier FC. Postoperative acute pulmonary edema: a rare presentation of pheochromocytoma. *Clin Nephrol* 1997; **48**: 122–4

24 Fink IJ, Reinig JW, Dwyer AJ *et al.* MR imaging of pheochromocytomas. *J Comput Assist Tomogr* 1988; **9**: 454–8

25 Frankel F von. Ein fall von doppelseitigem, vollig latent verlaufen Neben-nierentumor und gleichzeitiger Nephritis mit Veränderungen am Circulations-apparat und Retinitis. *Virchow's Arch Pathol Anat* 1886; **103**: 244–63

26 Geoghegan JG, Emberton M, Bloom SR, Lynn JA. Changing trends in the management of phaeochromocytoma. *Br J Surg* 1998; **85**: 117–20

27 Gorlin RJ, Sedano HO, Vickers RA, Cervenka J. Multiple mucosal neuromas, pheochromocytoma and medullary carcinoma of the thyroid—a syndrome. *Cancer* 1969; **22**: 293–9

28 Graham RM, Pettinger WA. Effects of prazosin and phentolamine on arterial pressure, heart rate, and renin activity. Evidence in the conscious rat for the functional significance of the pre-synaptic alpha-blockade. *J Cardiovasc Pharmacol* 1982; **4**: 44–52

29 Gutman Y, Boonyaviroj P. Mechanism of PGE$_1$ inhibition of catecholamine release from adrenal medulla. *Eur J Pharmacol* 1979; **55**: 129–36

30 Hamaji M, Oka N, Tashiro C, *et al.* Anaesthetic management with morphine in phaeochromocytoma. *Can Anaesth Soc J* 1984; **31**: 681–3

31 Hamilton A, Sirrs S, Schmidt N, Onrot J. Anaesthesia for phaeochromocytoma in pregnancy. *Can J Anaesth* 1997; **44**: 654–7

32 Hamilton CA, Dalrymple H, Reid JL. Recovery *in vivo* and *in vitro* of α_1-adrenoceptor responses and radioligand binding after phenoxybenzamine. *J Cardiovasc Pharmacol* 1982; **4** (Suppl 1): S125–8

33 Hamilton CA, Reid JL, Sumner DJ. Acute effects of phenoxybenzamine on α-adrenoceptor responses *in vivo* and *in vitro*: relation of *in vivo* pressor responses to the number of specific adrenoceptor binding sites. *J Cardiovasc Pharmacol* 1983; **5**: 868–73

34 Heramalsu K, Takahashi K, Kanemoto N, Arimori S. A case of pheochromocytoma with transient hyperinsulinemia and reactive hypoglycemia. *Jpn J Med* 1987; **26**: 88–90

35 Hoffman BB, Lefkowitz RJ. Catecholamines, sympathomimetic drugs and adrenergic receptor antagonists. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. *The Pharmacological Basis of Therapeutics*, 9th edn New York: McGraw-Hill 1995; 199–247

36 Hopkins PM, McDonald R, Lyons G. Caesarean section at 27 weeks gestation with removal of phaeochromocytoma. *Br J Anaesth* 1989; **63**: 121–4

37 Hull CJ. Phaeochromocytoma: diagnosis, pre-operative preparation, and anaesthetic management. *Br J Anaesth* 1986, **58**: 1453–68

38 Ibsen H, Rasmussen K, Jensen HE, Leth A. Changes in plasma volume and extracellular fluid volume after addition of prazosin to propranolol treatment in patients with hypertension. *Scand J Clin Lab Invest* 1978; **38**· 425–9

39 Imperato-McGinley J, Gautier T, Ehlers K, Zullo MA, Goldstein DS, Vaughan DE Jr. Reversibility of catecholamine-induced dilated cardiomyopathy in a child with pheochromocytoma. *N Engl J Med* 1987; **316**: 793–7

40 Iseri LT, Henderson HW, Derr JW. Use of adrenolytic drug, regitine, in pheochromocytoma *Am Heart J* 1951; **42**: 129–36

41 Jalil ND, Pattou FN, Combemale F, *et al.* Effectiveness and limits of pre-operative imaging studies for localisation of pheochromocytomas and paraganglionomas: a review of 282 cases. *Eur J Surg* 1998; **164**: 23–8

42 James MFM. Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma: a review of 17 anaesthetics. *Br J Anaesth* 1989; **62**: 616–23

43 James MFM, Huddle KRL, Owen AD, van der Veen BW. The use of magnesium sulphate in the anaesthetic management of phaeochromocytoma in pregnancy. *Can J Anaesth* 1988; **35**: 178–82

44 James TN. De subitaneis mortibus. XIX. On the cause of sudden death in pheochromocytoma with special reference to the pulmonary arteries, the cardiac conduction system and the aggregation of platelets. *Circulation* 1976; **54**: 348–56

45 Jebara VA, Uva MS, Farge A *et al.* Cardiac pheochromocytomas. *Ann Thorac Surg* 1992; **53**. 356–61

46 Joffe D, Robbins R, Benjamin A. Caesarean section and phaeochromocytoma resection in a patient with von Hippel–Lindau disease. *Can J Anaesth* 1993; **40**. 870–4

47 Jones DH, Reid JL, Hamilton CA, Allison DJ, Welbourn RB, Dollery CT. The biochemical diagnosis, localization and follow up of phaeochromocytoma: the role of plasma and urinary catecholamine measurements. *Q J Med* 1980; **49**: 341–61

48 Karlberg BE, Hedman L. Value of clonidine suppression test in the diagnosis of phaeochromocytoma *Acta Med Scand* 1986; **714** (Suppl): 15–21

49 Khafagi FA, Shapiro B, Fig LM, Mallette S, Sisson JC. Labetalol reduces iodine-131 MIBG uptake by pheochromocytoma and normal tissue. *J Nucl Med* 1989; **30**: 481–9

50 Khairi MRA, Dexter RN, Burzynski NJ, Johnston CC. Mucosal neuroma, pheochromocytoma and medullary thyroid carcinoma: multiple endocrine neoplasia type 3. *Medicine* 1975; **54**: 89–112

51 Langer SZ. Presynaptic regulation of the release of catecholamines. *Pharmacol Rev* 1981; **32**: 337–62

52 Lenders JWM, Sluiter HE, Thein T, Willemsen J. Treatment of a phaeochromocytoma of the urinary bladder with nifedipine. *Br Med J* 1985; **290**: 1624–5

53 Lippmann M, Ford M, Lee C, *et al.* Use of desflurane during resection of pheochromocytoma. *Br J Anaesth* 1994; **72**: 707–9

54 Lishajko F. Releasing effect of calcium and phosphate on catecholamines, ATP, and protein from chromaffin cell granules. *Acta Physiol Scand* 1970; **79**: 575–84

55 Loh KC, Shlossberg AH, Abbott EC, Salisbury SR, Tan M-H. Phaeochromocytoma: a ten year survey. *Q J Med* 1997; **90**: 51–60

56 McManus BM, Fleury TA, Roberts WC. Fatal catecholamine crisis in pheochromocytoma, curable cause of cardiac arrest. *Am Heart J* 1981; **102**· 930–2

57 Manger WM, Gifford JW Jr. Phaeochromocytoma: a clinical overview. In· Swales JD ed. *Textbook of Hypertension*. Oxford: Blackwell Scientific, 1994; 941–58

58 Mann C, Millat B, Boccara G, Atger J, Colson P. Tolerance of laparoscopy for resection of phaeochromocytoma. *Br J Anaesth* 1996; **77**: 654–7

59 Mathys H, Doshan HD, Rhule H *et al.* The bronchosparing effect of celiprolol, a new beta$_1$ alpha$_2$ receptor antagonist on pulmonary function of propranolol sensitive asthmatics. *J Clin Pharmacol* 1985; **25**: 354–9

60 Matsuyuki D, Kazuyuki I. Sevoflurane anesthesia with adenosine triphosphate for resection of pheochromocytoma. *Anesthesiology* 1989, **70**: 360–3

61 Mihai R, Farndon JR. Familial endocrine disease—genetics and early treatment. In: Farndon JR, ed. *A Companion to Specialist Surgical Practice*, Vol 5: *Breast and Endocrine Surgery*. London: W. B. Saunders, 1997; 113–42

62 Millard RK, Hutton P, Pereira E, Prys-Roberts C. On using a self-tuning controller for blood pressure regulation during surgery in man. *Comput Biol Med* 1987; **17**: 1–18

63 Millard RK, Monk CR, Prys-Roberts C. Self-tuning control of hypotension during ENT surgery using a volatile anaesthetic. *IEE Proc D* 1988; **135**: 95–105

64 Mugawar M, Rajender Y, Purohit AK *et al.* Anesthetic management of von Hippel–Lindau syndrome for excision of cerebellar haemangioblastoma and pheochromocytoma surgery. *Anesth Analg* 1998, **86**: 673–4

65 Mulligan LM, Kwok JBJ, Healey CS, *et al.* Germline mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A *Nature* 1993; **363**: 458–60

66 Mulligan LM, Marsh DJ, *et al.* Genotype–phenotype correlation in MEN 2: report of the International RET mutations consortium. *J Int Med* 1995; **238**: 343–6

67 Munro J, Hurlbert BJ, Hill GE. Calcium channel blockade and uncontrolled blood pressure during phaeochromocytoma surgery. *Can J Anaesth* 1995; **42**: 228–30

68 Muntz HH, Ritchey JO, Gatch WD. Adrenalin producing tumor (pheochromocytoma) containing 2300 mg of adrenalin. *Ann Int Med* 1947, **26**: 133–147

69 Nicholas E, Deutschman CS, Allo M, Rock P. Use of esmolol in the intraoperative management of pheochromocytoma. *Anesth Analg* 1988; **67**: 1114–7

70 Nicholson JP, Vaughn ED, Pickering TG, *et al.* Pheochromocytoma and prazosin. *Ann Int Med* 1983; **99**: 477–9

71 Pearse AGE. Cytochemical evidence for the neural crest origin of mammalian ultimobranchial C cells *Histochemie* 1971; **27**: 96–102

72 Pereira E. Adaptive closed-loop control of arterial pressure during anaesthesia. PhD Thesis, University of Bristol, 1988

73 Perel Y, Sclumberger M, Marguerite G, *et al.* Pheochromocytoma and paraganglionoma in children: a report of 24 cases of the French Society of Pediatric Oncology. *Pediatr Hematol Oncol* 1997; **14**: 413–22

74 Pick L Das Ganglioma embryonale sympathicum (sympathoma embryonale), eine typische bosärtige Geschwultsform des sympathischen Nervensystems. *Berl Klin Wochenschr* 1912, **49**: 16–22 (also *Verh Berl Med Ges* 1912; **13**: 522–57)

75 Pivalizza EG. Magnesium sulfate and epidural anesthesia in pheochromocytoma and severe coronary artery disease. *Anesth Analg* 1995, **81**: 414–6

76 Proye C, Thevenin D, Cecat P, *et al.* Exclusive use of calcium channel blockers in preoperative and intraoperative control of pheochromocytomas: hemodynamics and free catecholamine assays in ten consecutive patients. *Surgery* 1989, **106**: 1149–54

77 Prys-Roberts C, Farndon JR Doxazosin versus phenoxybenzamine in the perioperative management of patients with phaeochromocytoma. Submitted to *Clinical Endocrinology*.

78 Russell WJ, Metcalfe IR, Tonkin AL, Frewin DB. The preoperative management of phaeochromocytoma. *Anaesth Intens Care* 1998; **26**: 196–200

79 Ryan T, Timoney A, Cunningham AJ. Use of transoesophageal echocardiography to manage beta-adrenoceptor block and assess left ventricular function in a patient with phaeochromocytoma. *Br J Anaesth* 1993; **70**: 101–3

80 Saad MF, Frazier OH, Hickey RC, Samaan NA. Intrapericardial pheochromocytoma. *Am J Med* 1983; **75**: 371–6

81 Schuttler J. Quantitative assessment of catecholamine secretions as a rational principle of anaesthesia management in phaeochromocytoma surgery. *Anesth Intens Notfall Schmerz* 1995, **30**: 341–9

82 Serfas D, Shoback DM, Lorell BH. Phaeochromocytoma and hypertrophic cardiomyopathy: apparent suppression of symptoms and noradrenaline secretion by calcium-channel blockade. *Lancet* 1987; **ii**: 711–3

83 Shapiro JD, El Ganzouri A, White PF, Ivankovich AD. Midazolam–sufentanyl anaesthesia for phaeochromocytoma resection. *Can J Anaesth* 1988; **35**: 190–4

84 Shepherd JJ. The natural history of multiple endocrine neoplasia type I; highly uncommon or highly unrecognized? *Arch Surg* 1991; **126**: 935–52

85 Sipple JH. The association of pheochromocytoma with carcinoma of the thyroid gland. *Am J Med* 1961; **31** 163–6

86 Smyth P, Pringle S, Jackson G, Lorimer AR 24 hour control of blood pressure by once daily doxazosin: a multicentre double-blind comparison with placebo. *Eur J Clin Pharmacol* 1988; **34**: 613–8

87 Steiner AL, Goodman AD, Powers SR Study of a kindred with pheochromocytoma, medullary thyroid carcinoma, hyperparathyroidism, and Cushing's disease: multiple endocrine neoplasia, type 2. *Medicine* 1968, **47**: 371–409

88 Stenström G, Haljamae H, Tisell L-E. Influence of pre-operative treatment with phenoxybenzamine on the incidence of cardiovascular reactions during anaesthesia and surgery for phaeochromocytoma *Acta Anaesthesiol Scand* 1985; **29**. 797–803

89 Stowers SA, Gilmore P, Stirling M, *et al.* Cardiac pheochromocytoma involving the left main coronary artery presenting with exertional angina. *Am Heart J* 1987; **114** 423–7

90 Strebel S, Scheidegger D. Propofol–fentanyl anesthesia for pheochromocytoma resection. *Acta Anaesthesiol Scand* 1991; **35**: 275–7

91 Stringel G, Ein SH, Creighton R, *et al.* Pheochromocytoma in children: an update. *J Pediatr Surg* 1980, **15**: 496–500

92 Sutton H, Wyeth P, Allen AP, *et al.* Disseminated malignant phaeochromocytoma, localization with iodine-131-labelled meta-iodobenzylguanidine. *Br Med J* 1982; **285**: 1153–4

93 Takahashi K, Sai Y, Nosaka S. Anaesthetic management of Caesarean section combined with removal of phaeochromocytoma. *Eur J Anaesthesiol* 1998; **15**. 364–6

94 Takimoto E, Ueda W. Unsuspected pheochromocytoma of the urinary bladder. *Anesth Analg* 1995; **80** 1243–4

95 Thrasher JB. Phaeochromocytoma of urinary bladder: contemporary methods of diagnosis and treatment options *Urology* 1993; **41**: 435–9

96 Tjeuw M, Fong J. Anaesthetic management of a patient with a single ventricle and pheochromocytoma. *Anaesth Intens Care* 1990; **18**: 567–9

97 Vance JE, Buchanan KD, O'Hara D, Williams RH, Porte D. Insulin and glucagon responses in subjects with pheochromocytoma, effect of alpha adrenergic blockade. *J Clin Endocrinol* 1969; **29**: 911–6

98 Vincent J, Meredith PA, Reid JL, Elliott HL, Rubin PC Clinical pharmacokinetics of prazosin—1985. *Clin Pharmacokinet* 1985; **10**: 144–54

99 Von Euler US, Lishajko F. Effects of Mg^{2+} and Ca^{2+} on noradrenaline release and uptake in adrenergic nerve granules in different media. *Acta Physiol Scand* 1973; **89**: 415–22

100 Wallace JM, Gill DP. Prazosin in the diagnosis and management of phaeochromocytoma. *J Am Med Assoc* 1978; **240**. 2752–3

101 Welbourn RB. Early surgical history of phaeochromocytoma. *Br J Surg* 1987; **74**: 594–6

102 Wermer P. Endocrine adenomatosis and peptic ulcer in a large kindred. Inherited multiple tumors and mosaic pleiotropism in man. *Am J Med* 1963; **35**: 205–12

103 Wieland DM, Wu J-I, Brown LE, *et al.* Radiolabelled adrenergic blocking agents: adrenomedullary imaging with [^{131}I]iodobenzylguanidine. *J Nucl Med* 1980; **21**: 349–53

104 Wilner KD, Ziegler MG. Effects of alpha-1-inhibition on renal blood flow and sympathetic nervous activity in systemic hypertension. *Am J Cardiol* 1987; **59**: 82G–86G

105 Zakowski M, Kaufman B, Berguson P, Tissot M, Yarmush L, Turndorf H. Esmolol use during resection of pheochromocytoma. *Anesthesiology* 1989; **70**: 875–7

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Hormones and the gut

A. Holdcroft

Imperial College School of Medicine, Hammersmith Hospital, London W12 0HS, UK

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The heterogeneous hormones produced by the gastrointestinal tract control digestion. They are secreted from cells that line the lumen of the gut, that is, in the mucosa as well as in endocrine organs such as the pancreas. The major secretory and motor functions of the peptide hormones of the gut are listed in Table 1. Gut hormones also regulate cell growth. A few peptides, such as substance P and pancreatic polypeptide, are recognized as gut hormones but their function is uncertain. However, they can be secreted by endocrine tumour cells and may be responsible for some of their systemic manifestations.

Significant events in the discovery, localization and management of endocrine neoplasia from the gut are summarized in Table 2.[18] Initial reports came from biopsy or autopsy. Clinically defined syndromes followed. Then radioimmunoassay methods were developed, which identified gut hormones in 1961. Next, antagonists were synthesized and then markers for gut hormones and recently, in the 1990s, genetic screening for multiple endocrine neoplasias (MEN) was developed.[7]

Endocrine tumours are described as either 'non-functioning' or 'functioning', depending on their endocrine secretory activity. Excessive hormone production can be characterized by clinical syndromes. The two main examples are Zollinger–Ellison and carcinoid syndromes. Therapeutic advances through somatostatin analogues and interferon α (IFNα) have enabled symptom control, though with significant side-effects. Identification of genetic factors associated with MEN will significantly change clinical practice for surgeons and anaesthetists. In the past these tumours were usually diagnosed after patients presented with systemic manifestations. In the future, prophylactic elective surgery combined with lifelong surveillance may be required, perhaps at a young age, in order to prevent tumour occurrence.

The anaesthetic management of patients with abnormalities of gut hormone function induced by such tumours broadly requires an assessment of endocrine dysfunction (which may complicate anaesthesia and drug therapies), preferably with a standardized battery of tests for gut hormones. The spread of tumour growth by direct invasion or metastases also needs to be assessed in order to quantify organ dysfunction. For example, pancreatic endocrine tumours secrete vasoactive substances, leading to haemodynamic instability, and block the biliary system, resulting in obstructive jaundice. Recent developments in imaging technologies, such as the placement of biliary stents, hepatic artery embolization, radioisotopes of somatostatin for precise imaging of tumour location by scintigraphy and medical therapies to restrict tumour growth with targeted chemotherapy, enable improvements in organ function and symptomatic control to be achieved before anaesthesia and allows surgical targets to be identified in advance. Tumours limited to one part of the gastrointestinal tract can potentially be completely removed by surgery and even palliative surgery can provide an improved quality of life by reducing hormone secretion, thus potentiating the use of somatostatin analogues. If the tumour shows no somatostatin receptors on imaging, histological confirmation of this can limit the side-effects of somatostatin analogue therapies, which would otherwise be administered. However, not all patients have these types of tumours diagnosed before surgery. Anaesthetists should therefore be alert for the rare causes of bronchospasm, such as carcinoid tumours.

Multiple endocrine neoplasia

Patients with MEN have two or more endocrinopathies. This diagnosis may be difficult to make because the endocrine presentations may occur at different times. In a review of cases from Hammersmith Hospital, secondary endocrine syndromes (particularly gastrinoma) occurred in 7% of 353 patients up to 10 years after diagnosis of the first syndrome.[54] This time interval has led to one of the main problems in the diagnosis of MEN.[36] Another reason for a lack of recognition and understanding of the frequency of this condition has been in the availability of diagnostic tests. It is only in the past 10 years that genetic screening has enabled clinicians to distinguish between the MEN syndromes. These genetically linked lesions are found not only in the endocrine pancreas, the thyroid, the parathyroid and

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Table 1 Peptide hormones of the gastrointestinal tract GIP=gastric inhibitory peptide (glucose insulinotrophic peptide), LOS=lower oesophageal sphincter, VIP=vasoactive intestinal peptide. *Also occur as neurotransmitters in the plexuses of the gut

Hormone	Produced by	Major function(s)
Gastrin	Gastric antrum, duodenum	Acid secretion, contraction of LOS, secretion of glucagon
Secretin	Mucosa	Pancreatic secretion of water and electrolytes
Cholecystokinin*	Mucosa	Gall bladder and pancreatic secretion
GIP	Mucosa	Inhibits gastric acid secretion
Motilin	Mucosa	Contraction of LOS
Pancreatic polypeptide	Pancreas	Unknown
Peptide tyrosine	Mucosa	Decreases gastric acid secretion
Substance P*	Mucosa, nerves	Unknown
Neurotensin	Mucosa	Delays gastric emptying
Somatostatin*	Gastric antrum, pancreatic δ cells	Endocrine/paracrine; inhibits secretion of gastrin, secretin, GIP, motilin, pancreatic polypeptide, pancreatic secretion, glucagon, insulin
VIP*	Nerve cells, endocrine cells	Pancreatic secretion
Glucagon	Pancreatic α cells	Stimulates release of insulin and pancreatic somatostatin
Insulin	Pancreatic β cells	Anabolic hormone
Histamine	Mast cells close to parietal cells	Attaches to H_2 receptors and sensitizes cell to stimuli such as gastrin
Calcitonin	Oesophageal tumour	Not normally produced in the gastrointestinal tract

Table 2 Significant events in the discovery of endocrine neoplasias from the gastrointestinal tract

Type of neoplasm	Date	Event
Carcinoid tumour	1888	Identified at autopsy
	1907	Oberndorfer introduced the term 'carcinoid'
	1954	Carcinoid syndrome described
Insulinoma	1927	First diagnosed at autopsy
	1938	Whipple's triad
Gastrinoma	1955	Zollinger and Ellison first described syndrome of recurrent peptic ulcers
	1960	Gastrin identified as the secretory product of the islet cell tumour in Zollinger–Ellison syndrome
VIPoma	1958	Verner–Morrison syndrome described
	1973	VIPoma identified
Glucagonomas	1942	First described
MEN1	1954	Wermer identified familial occurrence (autosomal dominant) of tumours of pituitary, parathyroid and endocrine pancreas
	1997	Discovery of multiple endocrine adenomatosis (MEA-1) gene

the pituitary organs but also in the adrenal and in the intestine, particularly as submucosal duodenal carcinoid tumours. MEN2A (Sipple syndrome) is associated with multifocal medullary thyroid cancer and occasional bilateral benign phaeochromocytomas. MEN2B (Gorlin or Steinert syndrome) is the rarest, probably because the associated medullary thyroid cancer is most aggressive. MEN1 (Wermer syndrome) is an autosomal dominant condition with the gene located on chromosome 11. Only the pancreatic and duodenal tumours have a strong tendency to malignancy. Tumours can be functional or non-functional; the relative occurrence is shown in Table 3.[20] Tumours can change the expression of peptide secretion and one hormonal secretion may replace another. Gastrinomas are the most common functional pancreatic tumours in MEN1 and tumours should be removed only after adequate control of gastric secretion by proton-pump inhibitors. Prophylactic pancreatectomy for MEN1 is not currently indicated, neither is diagnostic laparoscopic surgery because lesions are multiple and preoperative imaging techniques often require supplementary identification of tumours by manual palpation and intra-operative ultrasonography.

Pancreatic endocrine tumours

The endocrine pancreas consists of the islets of Langerhans, which occur throughout the pancreatic tissue, particularly in the tail of the pancreas. Within the islets, the α cells occur external to the δ cells while the β cells lie at the centre. Hormones from the islet cells are secreted into the blood stream but also diffuse locally within the islets. The arrangement and functional interactions of these secretory groups within the islets are not fully understood nor can all the clinical manifestations of their secretory tumours be associated with the limited number of hormones identified at present. The α cells, which comprise 20–25% of the islet cells, secrete glucagon. The β cells occur with the highest frequency (60–80%) and secrete insulin. The δ cells are the least common (10–15%) and secrete somatostatin. An unknown proportion of cells secrete pancreatic polypeptide. The islets are part of the amine precursor uptake and decarboxylation (APUD) cell system, which takes up amine precursors, decarboxylates them to form amines and synthesizes a variety of peptides.[50]

Tumours of the pancreatic islet cells secrete one or more hormones and are termed apudomas. These hormones can

Table 3 Clinical presentations of MEN 1, listed in order of frequency. *Frequency of diagnoses from screening (16%) to autopsy (100%)

Incidence	Location	
Incidence ↑	*Most frequent locations*	
>95%	Parathyroid hyperplasia	
80-100%	Pancreatic endocrine tumours →	↑ non-functional
16-100%*	Anterior pituitary adenomas (e g prolactinoma)	gastrinoma
30%	Adrenal adenomas	insulinoma
13-30%	Gastric carcinoids	
7%	Lung carcinoids	glucagonoma VIPoma
	Least frequent	somatostatinoma

be ones that are normally secreted by the pancreas, or they can be non-pancreatic hormones, such as adrenocorticotrophic hormone. Approximately 75% of apudomas are insulinomas (incidence of one to four cases per million people). About 20% of apudoma patients will have MEN1 and the pancreatic endocrine tumours listed in Table 3 in order of frequency, with, in addition, tumours of the parathyroid, pituitary and rarely adrenal cortex.

Non-functioning neuroendocrine tumours of the pancreas may be silent because they produce hormones without specific clinical signs or because they produce peptides in insignificant amounts, or none at all. They are large in size and vascular.[5] Resection, even if incomplete, is often associated with prolonged survival and, since these tumours respond poorly to chemotherapy, surgery is the treatment of choice.

Strategies to control tumour growth are required if the tumour is growing quickly or if symptoms are severe. The number of ways of treating such tumours has increased rapidly over the past decade. Tumour debulking makes symptoms easier to manage and allows further treatment to reduce tumour mass by chemotherapy. Other therapies include hepatic artery embolization, treatment with somatostatin analogues, IFNα, combination therapies with somatostatin and IFNα, or occasionally systemic chemotherapy or liver transplantation. The rarity and variety of endocrine syndromes have necessitated the development of multicentre clinical trials in tertiary referral centres to support evidence-based treatments.

Gastrinoma

Zollinger–Ellison syndrome was described as intractable, painful, peptic ulcer disease that recurs after surgery unless total gastrectomy is performed. Duodenal, pancreatic or rarely ovarian cystadenocarcinoma cells releasing gastrin cause the clinical syndrome. In the pancreas it is the δ islet cells which produce gastrin. Diarrhoea and steatorrhoea leading to weight loss often occur as a result of excess acid production, which inactivates pancreatic enzymes. Less frequently, dysphagia presents secondary to oesophagitis. A concentration of gastrin of >100 pg ml^{-1} in a fasting basal state is diagnostic of a gastrinoma. However, anything that decreases gastric acid production can lead to high circulating concentrations of gastrin; this includes drug treatment with H_2 receptor antagonists (such as cimetidine) and hydrogen ion (proton) pump blockers (such as omeprazole), as well as diseases such as pernicious anaemia. Thus, to prevent confusion, this type of drug treatment should be withdrawn before diagnostic tests for gastrinoma. If there is any uncertainty, provocative tests with calcium or secretin may be required.

Although medical treatment can control acid secretion, tumour excision for sporadic tumours has a high overall survival rate.[34] The role of surgery in Zollinger–Ellison syndrome associated with MEN1 is less clear. Measurement of serum calcium concentrations and plasma parathyroid hormone or pituitary hormone studies may confirm the diagnosis of MEN1. In the future, specific genetic screening may be required because of the difference in prognosis between sporadic and MEN1 gastrinomas.

Preparation for surgery requires titration of the dose of proton-pump inhibitors, such as omeprazole or lansoprazole, to achieve normal basal gastric acid secretion. Oral medications are preferred rather than somatostatin, which has to be administered subcutaneously. Antacid prophylaxis with proton-pump inhibitors and H_2 receptor antagonists should be maintained until surgery. The possibility of anaemia from bleeding gastric ulceration must be investigated. A full coagulation screen and liver function tests are required because alterations in fat absorption may influence clotting factors and hepatic function may be disturbed by liver metastases. Immediately before and after operation, intravenous ranitidine is useful to prevent gastric acid hypersecretion from the hypertrophied acid-producing gastric mucosa. A nasogastric tube will be required perioperatively; it should be placed and its position confirmed at induction of anaesthesia. At exploratory laparotomy, further localization of pancreatic or duodenal gastrinomas may be required using palpation, transillumination, ultrasound and endoscopy. These processes may increase the surgical exposure required to mobilize these structures and hence may increase the duration of surgery. Anaesthetic planning should include preparations to reduce heat loss during prolonged surgery.

Insulinoma

Tumours of the β cells of the pancreas secrete insulin; patients with such tumours present with episodic symptoms of fasting hypoglycaemia, such as dizziness, blurred vision, confusion, irritability, tremors and occasionally coma. Compensatory sympathetic mechanisms lead to sweating and tachycardia. The differential diagnosis is broad; the causes of hypoglycaemia listed in Table 4 should be excluded, together with other aetiologies such as cerebro-

Table 4 Causes of hypoglycaemia to be considered in the differential diagnosis of insulinoma

Cause	Example(s)
Drug effects	Ethanol, quinine and sulphonylureas
Enzyme deficiencies	Glycogen storage disease
Hormone deficiency	Addison's disease
Illness	Sepsis and liver failure
Others	Intense exercise

vascular disorders. About 8% of insulinomas are associated with MEN1. The diagnosis is made by 'Whipple's triad':[49] (i) symptoms of hypoglycaemia; (ii) a low plasma glucose; and (iii) relief of symptoms when glucose is administered and normal glucose levels restored. The diagnosis is made by a fasting plasma glucose of <2.2 mmol litre^{-1}, increased insulin ($\geqslant 6$ μunits ml^{-1}; >40 pmol litre^{-1}), increased C-peptide ($\geqslant 0.2$ nmol ml^{-1}) and an absence of sulphonylurea in the plasma.[11] [25] The high insulin and C-peptide concentrations confirm the diagnosis. These two compounds are formed in equimolar amounts by enzymatic cleavage of proinsulin. Measurable C-peptide therefore indicates an endogenous source of insulin, in contrast with the use of a pharmaceutical preparation of insulin that may be used to mimic the symptoms of an insulinoma.

Insulinomas are rare, mainly single, located in the pancreas and small in size (and thus sometimes difficult to locate); on enucleation, few recur. More radical surgery, including hepatic resection, is required for malignancy in a small number of patients. Medical therapies will be initiated before surgery. Frequent meals can prevent symptoms. However, drugs that inhibit insulin release are not effective. These include glucocorticoids, phenytoin and β-adrenergic blocking drugs. Somatostatin analogues have not been proven to be of value in reducing symptoms, perhaps because octreotide may reduce glucagon in addition to insulin secretion.

Diazoxide is a non-diuretic benzothiazide which inhibits the release of insulin from secretory granules of β cells. It may be a therapeutic option in preoperative preparation. Its use is usually restricted to situations where surgery has failed because it may not block secretion from abnormal (i.e. non-β) cells. It can also suppress the release of glucagon and exacerbate symptoms. Besides its unpredictable efficacy, diazoxide also has serious dose-dependent side-effects, causing oedema, sodium retention, hypotension, cardiac disturbances, weight gain and hirsutism. Verapamil, a calcium channel blocker, has been successfully used in long-term therapy when surgery was refused.[45]

Although most tumours are enucleated, the head or tail of the pancreas has to be exposed. Resection may sometimes be required, especially with MEN1, where the head of the pancreas often needs to be removed. The spleen is preserved whenever possible but splenectomy may be unavoidable. Planning for this will include vaccination against meningococcus and *Haemophilus influenzae* with Pneumovax and having blood cross-matched for transfusion. Prophylactic therapies include antibiotics and possibly somatostatin. In one of the largest studies of insulinomas, although no direct deaths were reported, complications of surgery included acute myocardial infarction, congestive cardiac failure and paroxysmal atrial tachycardia.[13] Assessment of cardiac function preoperatively and monitoring and maintenance of cardiac stability perioperatively are prerequisites for anaesthetic care.

It is essential that close monitoring of glucose intake and blood glucose is started the evening before surgery and continued throughout the perioperative period. During this period of starvation and at operation when the tumour is handled, glucose 50% solution should be available. Intravenous glucose with potassium should be infused and blood glucose, electrolytes and fluid input and output monitored at least hourly in order to avoid hypoglycaemia, water load and hyponatraemia. On tumour excision, a progressive increase in blood glucose has been described within minutes. Repeated measures of blood glucose and maintenance of normal values are more important than the observation of rebound hyperglycaemia which used to be a marker of complete tumour resection.[31]

The choice of anaesthetic agents for removal of an insulinoma has focused on their effects on blood glucose. Methoxyflurane has been used[4] because it tends to increase blood glucose concentrations. More recently, sevoflurane has been recommended because it is considered to suppress the spontaneous release of insulin.[29] However, the metabolic profile of isoflurane should be considered an advantage, particularly if liver blood flow or liver function is disturbed. Another technique that has been reported not to interfere with blood glucose control is general anaesthesia, using propofol, combined with epidural analgesia.[40]

Postoperative complications that may alter blood glucose homeostasis include diabetes mellitus as a result of pancreatic insufficiency, acute pancreatitis and intra-abdominal abscesses. Pancreatic fistula is a serious complication because it can lead to electrolyte imbalance and the need for further surgery.

Glucagonomas

The α cells of the pancreas release glucagon. The two clinical diagnostic features of glucagonomas are an erythematous rash and diabetes mellitus. The rash, presenting in the groin and perineum and then migrating to the distal extremities, is known as necrotizing migratory erythema; it may be treated with zinc ointments. Stimulation of hepatic glycogenolysis and gluconeogenesis results in the metabolic production of glucose and symptoms of diabetes mellitus. However, ketoacidosis is rare because insulin concentrations are also increased. Tumours are associated with weight loss, glossitis, stomatitis, anaemia (probably from bone marrow suppression), reduced

Table 5 The symptoms and signs of VIPomas and their main causes

Symptom/sign	Cause(s)
Diarrhoea	VIP stimulated
Hypokalaemia	Passive K^+ loss in stool, active K^+ secretion by colon secondary to hyperaldosteronism
Hypochlorhydria	Inhibition of gastric mucosal function
Metabolic acidosis	Excess HCO_3^- loss
Flushing	VIP vasodilation
Hyperglycaemia	VIP glycogenolysis (structurally similar to glucagon)
Hypercalcaemia (tetany)	Hyperparathyroidism, acidosis
Hypomagnesaemia (tetany)	Loss in stool

blood amino acid concentrations and diarrhoea. If the cachexia is severe and the patient is malnourished, nutritional support and supplements for several weeks before surgery should be given, otherwise infection and poor wound healing are likely to occur postoperatively.

A blood glucagon concentration of $\geqslant 50$ pg ml^{-1} and a demonstrable tumour are diagnostic of glucagonoma. The increase in glucagon should be differentiated from the increases measured in prolonged fasting or renal and hepatic failure. The tumour may be primary, in an elderly population, or associated with other syndromes such as Zollinger–Ellison and MEN1 and present in younger patients. The majority of patients have liver metastases at presentation. Treatment is by debulking and somatostatin analogues, which give rapid relief at first but increased dosage may be necessary later. There is an increased incidence of venous thromboses in this disease and prophylactic antithrombotic therapy is appropriate. Once the tumour is excised, symptomatic relief is achieved.

Somatostatinomas

Tumours of the δ cells may release somatostatin and are often misdiagnosed as adenocarcinomas. Patients with such tumours present commonly with obstructive biliary disease because many pancreatic tumours are large. Obstructive jaundice should be relieved by stenting before surgery so that complications, such as coagulopathies and postoperative renal failure, are avoided. Other symptoms are usually mild. These include diabetes, from a reduction in insulin release, steatorrhoea from decreased pancreatic enzyme secretion and gallstones resulting from stasis within the gall bladder. Somatostatinomas can present in association with phaeochromocytomas and von Recklinghausen's disease in the MEN2 syndrome.

VIPoma

Verner–Morrison or WDHA (watery diarrhoea, hypokalaemia, achlorhydria) syndrome is characterized by profuse watery diarrhoea, intestinal ileus, abdominal distension, confusion, drowsiness, hypokalaemia, achlorhydria, hypomagnesaemia, metabolic alkalosis and tetany (Table 5). It is very rare. The mediator is vasoactive intestinal peptide (VIP), which should be measured accurately in order to establish the diagnosis. VIP inhibits gastrin release. Pancreatic VIPomas are commonly located in the body and tail of the organ while extra-pancreatic VIPomas occur in the autonomic nervous system. The rate of malignancy warrants resection because 40% of VIPomas are benign and the others are slow growing, commonly with liver metastases. The tumours are vascular and are usually localized on routine imaging. Care should be taken when injecting contrast media because VIP may be released. Medical treatment includes somatostatin analogues, which inhibit both VIP release and the secretion of water and electrolytes from the gastrointestinal tract.

The primary abnormality is dehydration from stimulation of intestinal secretions with fluid losses (rich in potassium) of 3–10 litres day^{-1}. The coexistence of VIPoma and gastrinoma in MEN1, both of which result in diarrhoea, should be checked by preoperative investigations and tumour localization. VIP relaxes smooth muscle and dilates splanchnic and peripheral vascular beds; it can induce hypotension from this mechanism as well as fluid losses from the circulating blood volume. In the past, patients have died because of a delay in diagnosis rather than from the tumour itself. Resuscitation in a critical care facility has a vital role in the management of such patients. Replacement of fluids with central venous pressure monitoring, electrolytes (such as potassium and magnesium) and correction of acidosis is the initial step. Blood glucose should also be maintained carefully. Control of the diarrhoea will then enable surgery to be planned. A positive response to somatostatin analogues is rapid, occurring within 24–48 h. If somatostatin treatment fails, other therapies that can be used include steroids such as methylprednisolone, indomethacin (a prostaglandin inhibitor) and metoclopramide. Once cardiovascular stability is achieved, preoperative preparation must include H_2 receptor blocking drugs to prevent rebound gastric acid hypersecretion.[2]

Carcinoid tumours

Carcinoid tumours were first described in 1888 at autopsy from multiple tumours in the distal ileum. They stain with silver stains and contain markers of neuroendocrine tissue, such as chromogranin and synptophysin. Within the cells there are numerous secretory granules containing hormones and amines including serotonin, corticotrophin, histamine, dopamine, substance P, neurotensin, prostaglandins and kallikrein (an enzyme which generates kinins from kininogen precursors, such as bradykinin and tachykinins). The tumours are no longer classified according to origin (fore-, mid- or hind-gut) but from their histology, site, function and biological characteristics.[3] They are commonly located not only in the gut (including the stomach, the appendix, the ileum and rectum) but also in the bronchi and lungs.[23]

Carcinoid cells secrete a variety of amine and peptide hormones, which may be identified biochemically using a standard battery of tests including high-pressure liquid chromatography for 5-hydroxyindole acetic acid (5-HIAA) and radioimmunoassay for glycogen, VIP, calcitonin, gastrin, pancreatic peptide and insulin. Bronchial carcinoids can produce an excess of adrenocorticotrophic hormone and growth hormone-releasing factor and may present as Cushing's syndrome or acromegaly. The secretory pattern of gut tumours can change over time; an anaesthetist should be aware of this preoperatively in order to interpret investigations. Tumour location is identified by non-specific investigations such as computerized tomography, magnetic resonance and ultrasound imaging; and somatostatin receptor scintigraphy or positron emission tomography with ^{11}C-labelled 5-hydroxytryptophan (the precursor of serotonin) are used for more specific localization. Symptomatic tumours are treated with surgery and drug therapy. Further diagnostic tests with histology and immunocytochemistry can determine the peptide profile of the tumour.

Gastric carcinoid tumours are divided into various types, which have different prognoses. Benign tumours arise from mucosal cells that synthesize and store histamine. They occur as multiple tumours in the fundus or body of the stomach and have been associated with 2–9% of patients with pernicious anaemia, and atrophic gastritis, situations in which gastrin concentrations are high. Tumours associated with MEN1 have a higher rate of malignancy. Those composed of a mixture of cell types are solitary and metastasize. They produce various hormones including neuroendocrine and exocrine pancreatic secretions.

Small bowel carcinoid tumours grow slowly. They can present with bowel obstruction from mesenteric fibrotic stricture, carcinoid syndrome, gastrointestinal bleeding, diarrhoea and weight loss. Arterial or venous obstruction by the tumour can lead to abdominal pain (angina) precipitated by food. Since carcinoid tumours are the commonest small bowel neoplasms, any small bowel obstruction should alert an anaesthetist to consider this diagnosis. The anaesthetist must prepare for emergency anaesthesia with precautions to prevent aspiration of stomach contents. During surgery the tumour site should be observed (for bleeding or manipulations) and cardiovascular instability treated with therapies, such as octreotide. Gross pathology may reveal a yellow nodule and frozen section histology may confirm the diagnosis.

Bronchial carcinoid tumours can present as a mass, atelectasis, unilateral lung hyperinflation (from a ball-valve action) and with filling defects in the airways.[32] When major airways are affected, flow-volume and ventilation-perfusion abnormalities can be detected. At thoracotomy, surgery may be limited to a bronchial wedge resection or extend to a lobectomy, especially if suppuration has proceeded distal to the tumour or to a tracheal resection for tracheal obstruction. Airway maintenance during anaesthesia for these procedures can be a challenge.[21]

Carcinoid syndrome occurs secondary to the systemic release of secretions either as a result of metastasis in the liver or from the lung. Bronchial carcinoids can liberate substances directly into the circulation. It has been postulated[23] that when a carcinoid tumour releases active substances into the portal vein, the liver destroys them until either liver function deteriorates, or shunts between the portal and hepatic veins, or metastases developed. Thus general release of secretory products from the gastrointestinal tract is usually prevented until the portal system is bypassed. Substances released by carcinoid tumours include: serotonin (5-hydroxytryptamine), which is synthesized from 5-hydroxytryptophan and metabolized to 5-HIAA, which can be measured in urine; histamine, which is metabolized and excreted in the urine as tele-methylimidazoleacetic acid; tachykinins, such as substance P, neurokinin A and neuropeptide K, which causes flush and may be an early indicator of carcinoid disease;[33] bradykinins; and prostaglandins. Table 6 lists these mediators, their clinical effects and management.[28]

Skin manifestations were described in the original report of carcinoid syndrome[43] with changing, patchy red and cyanotic areas, plethoric in nature and flushing of the face and neck, exacerbated by hot food and spices. This eventually leads to enlarged veins and telangectasia with brown patches of hyperpigmentation on the face, wrist, back and thighs, similar to pellagra. The pellagra-like signs have been related to niacin deficiency, because dietary tryptophan is converted into 5-HIAA and can be treated by replacement therapy. The flush from pure histamine release differs from this, in that the face swells and lachrymation occurs. Severe facial oedema has been reported during anaesthesia but without airway difficulty.[26]

Common features of carcinoid syndrome are diarrhoea, from gastrointestinal hypermotility, and flushing, but neither usually requires resuscitative treatment. Diarrhoea may persist after surgery for resection of the terminal ileum because of a loss of bile acids. Thus when the patient is assessed preoperatively for any complications of surgery, this secondary complication should be considered and long-term electrolyte abnormalities sought.

It is the respiratory and cardiovascular effects of carcinoid syndrome with which an anaesthetist should be familiar because of their severity. Bronchoconstriction, which presents as wheezing and paroxysmal coughing, can be life-threatening and requires prophylactic treatment. Dyspnoea may be present but an underlying cardiac problem should be considered in addition to bronchoconstriction. Right ventricular failure, resulting from endocardial fibrosis, is a major cause of death in carcinoid syndrome. It is slow in onset and although cardiac oedema is reported, underdiagnosis occurs in clinical practice.[23] Echocardiography can confirm the presence of right ventricular dysfunction and tricuspid and pulmonary valve

Table 6 Clinical effects, mediators and treatment of carcinoid syndrome

Clinical effects	Proposed mediators	Treatment
Flushing	Tachykinins (neurokinin A, substance P, neuropeptide K)	Somatostatin analogues (others. interferon α, glucocorticoids, phenothiazines, α-adrenergic block, avoid alcohol)
	Histamine	H_1 and H_2 receptor blocking drugs (chlorpheniramine, ranitidine, cimetidine)
	Vasoactive peptides (VIP)	Somatostatin analogues
Hypotension		Check fluids, myocardial depressants, somatostatin analogues, angiotensin, vasopressin, methoxamine, (epinephrine – care!)
Diarrhoea	Serotonin (5HT) Prostaglandins E and F	Somatostatin analogues (others. parachlorphenylalanine, 5HT antagonists (cyproheptadine, methysergide, ondansetron), loperamide, interferon α)
	Bile acid loss	Cholestyramine
	Bacterial contamination	Doxycyclin
Abdominal cramps	Small bowel obstruction	Surgical decompression
Dyspnoea		
(a) wheezing (bronchoconstriction)	Serotonin Substance P Bradykinins	Somatostatin analogues, bronchodilators (care!); (β-adrenergic agonists, theophylline), chlorpheniramine, nebulized ipratropium bromide
(b) carcinoid heart disease	Growth factors, 5HT(?)	Valvular replacement (tricuspid, pulmonary), diuretics
Skin lesions (pellagra-like)	Niacin deficiency	Nicotinamide
Palpitations (tachycardia, hypertension)	Serotonin	Somatostatin analogues, ketanserin, (others: labetolol, esmolol, increased depth of anaesthesia)

lesions. These abnormalities are thought to result from the episodic circulatory crises associated with liberation of active substances from the tumour. 5-Hydroxytryptamine increases pulmonary artery pressure and intestinal peristalsis together with bronchoconstriction.[47] Intravenous substance P in humans causes flushing, tachycardia and hypotension[9 10] but is not considered to be the main active chemical responsible for carcinoid syndrome. Endocardial fibroelastosis has been linked to growth factors.[48] Such activity is part of the function of gut hormones. Sclerosis and partial fusion of cusps is the pathological result. It leads to tricuspid and pulmonary valve incompetence and stenosis and may even recur in bioprosthetic valves[39] used for valve replacement. Rarely, ascites and pleural effusion have been described. When considering anaesthetic monitoring, such valve damage may predispose to endocarditis, so pulmonary artery catheter insertion may be contraindicated.

Left-sided heart disease has also been described.[19] Carcinoid syndrome can therefore present as a critical crisis in addition to structural heart disease, with bronchoconstriction, tachycardia and hypotension or hypertension leading to cerebral hypoxia with confusion and coma. These acute cardiorespiratory events are most common during laparotomies and during or after embolization of liver metastases; in their differential diagnosis, acute anaphylaxis should be considered.[1] Unfortunately, there is no predictor of cardiovascular instability, such as peptide concentrations, so vigilance and early intervention are advised.

Therapeutic management, as shown in Table 6, targets symptoms or more specific mechanisms. Methylsergide in the past was used as a non-selective vasoactive agent, but it can cause fibrotic heart lesions. Codeine phosphate can be used to treat the diarrhoea, but fluid, electrolyte and nutritional deficiencies require replacement. Antibradykinin agents, such as aprotonin, used to be administered acutely during carcinoid tumour surgery. *In vitro*, aprotinin effectively inhibits kallikrein[22 26] but clinically it is not so effective.[28 46] Antiserotonin antagonists, including non-specific drugs, such as cyproheptadine[41] and parachlorophenylalanine,[35] and more specific antagonists, such as ketanserin (a $5HT_2$ antagonist[15 16 46]) and ondansetron (a $5HT_3$ antagonist), have been used to relieve symptoms.[51] However, the approach based on antagonizing released hormones has been largely superseded by a preference to inhibit hormone release.[38] Steroids have been used successfully to block substance release but more specific drugs based on somatostatin have been developed. Steroids may be indicated in asthmatic patients.[46] Generally, it is only when these somatostatin analogues fail to reduce symptoms adequately that antagonists are used in medical treatment. However, H_1 and H_2 receptor antagonists may be considered for preoperative prophylaxis and during surgery; where there is the potential for release of large quantities of hormones on tumour handling, judicious use of hormone antagonists should be considered.

Principles of management of gastrointestinal endocrine tumours

Experience in managing the complex problems associated with these endocrine tumours is limited mainly to retrospective reviews and case reports. Whenever possible, patients should be treated in tertiary centres with expertise in endocrine surgery, anaesthesia and perioperative critical care.

Somatostatin

The development of synthetic somatostatin analogues, such as octreotide (Table 7), that are long-acting and inhibit hormone release rather than block their action has revolutionized anaesthetic management, particularly for

Table 7 Characteristics of somatostatin and its analogues. *Slow intravenous injection

Characteristics	**Somatostatin**	**Somatostatin analogues**
Number of amino acids	14 or 28	8
Half-life (min)	<3	80–140
Route of administration	Intravenous* (infusion)	Intravenous*, subcutaneous (Octreotide), intramuscular (lanreotide)
Receptors activated	High affinity for all somatostatin receptor subtypes	distinct binding profiles (limits diagnosis and therapeutic use)
Post-infusion rebound hyperstimulation?	yes	no
Side effects (for both somatostatin and somatostatin analogues)	Pain at injection site Inhibition of hormone release (e.g. causing gallstones from cholecystokinin release) Reduces motility (presents as flatulence, abdominal cramps, diarrhoea) Blocks exocrine function (causes steatorrhoea by inhibiting pancreas secretion) Others (e.g. alopecia)	

carcinoid, glucagonoma and VIPoma tumours. Somatostatin binds to cell surface receptors, inhibits adenylyl cyclase and enhances potassium conductance, thus decreasing intracellular calcium ion availability and cellular secretion.[44] Somatostatin analogues do not bind to all somatostatin receptor subtypes; this limits their diagnostic and therapeutic use. In addition, long-term efficiency may be reduced by receptor down-regulation. Octreotide has to be given parenterally, for example as 100 µg subcutaneously every 8 h, or 100 µg h^{-1} during surgery. In an emergency a single dose of 50 µg i.v. before surgical manipulation may suffice if no preoperative prophylaxis has been given. Another beneficial preoperative effect of somatostatin is an indirect anti-angiogenesis activity that can reduce the size of metastases. The success of such specific therapies has enabled more aggressive surgery combined with medical treatments to improve survival rates.[42] There is no evidence to support the postoperative use of octreotide to prevent gastrointestinal complications,[24] but it may have a role in maintaining cardiovascular stability.

Types of surgery

A broad spectrum of patients present for major gastrointestinal and hepatic surgery.[12] Definitive resection of the tumour is the primary aim in order to secure a potential cure. Prophylactic cholecystectomy eliminates the possibility of gallstones developing during future octreotide therapy. The most common procedures for pancreatic endocrine tumours are pancreatoduodenectomy, distal pancreatectomy and enucleation; less commonly, resection of metastases is performed, often combined with medical and oncological therapies.[37] Palliative surgery to debulk tumours or relieve obstruction may be planned as an elective or emergency procedure. In the acute situation, time for preparation of patients with hormonally functioning tumours should be considered essential for optimal care. Large abdominal incisions and major tissue manipulations are to be expected, so the support of intensive care facilities and adequate postoperative pain relief are priorities for surgical and anaesthetic management.

Specific types of surgery may be required. The development of right-sided heart failure in carcinoid syndrome is an indication for tricuspid and pulmonary valve replacement. Significant morbidity and mortality in older patients has been described in valvular replacement in carcinoid syndrome.[6] Haemodynamic instability can be the result of endocrine secretion or treatment with somatostatin, which is a negative inotrope.[55] Treatment of hepatic metastases may be surgical. However, hepatic artery ligature and devascularization have a high mortality and survival from hepatic transplantation is disappointing. Occasionally, if metastases are well localized to a lobe, cytoreductive surgery is an acceptable option. Selective hepatic artery embolization is preferred for symptom relief. The acute tumour lysis that follows can generate severe systemic dysfunction for which intensive care management is the preferred option. Abnormalities of liver function are common and accompanied by fever, nausea, vomiting (ileus) and abdominal pain. Vasoactive peptides can be released and renal failure results from contrast load, fluid loss and cardiovascular disturbances such as hypotension. Prophylactic octreotide and broad-spectrum antibiotics are essential and secondary infection or infarction of gastrointestinal structures must be excluded.

Anaesthesia

Preoperative medical therapy with octreotide or a similar somatostatin analogue will provide prophylaxis against the risk of a carcinoid crisis. It may not prevent an overwhelming release of bronchoconstrictors or vasoactive substances during handling of the tumour at surgery. Preparations for anaesthesia, as summarized in Table 8, involve correction of

Table 8 Preoperative checklist for major pancreatic endocrine surgery

	Management
Medical syndromes	
Insulinoma	Glucose, diazoxide
Gastrinoma	Proton-pump inhibitors and H_2 receptor blockers preoperatively
VIPoma	Somatostatin analogues
Glucagonoma	Somatostatin analogues
Somatostatinoma	Somatostatin analogues
Carcinoid	Somatostatin analogues, serotonin antagonists
Surgical diagnosis	Localization, peptide secretion identified
Stomach	Nasogastric tube sited at induction
Emergency obstruction	Preoperative nasogastric suction and drainage, rapid sequence induction
Large surgical exposure	
Blood loss	Cross-match, coagulation screen, large-bore cannulae (e g 13 G), central venous and arterial catheters with direct pressure monitoring, blood warmers and infusors (capacity 1 litre min^{-1})
Potential hypothermia	Active and passive warming, temperature monitoring (core and periphery)
Pain	Epidural (thoracic) or patient-controlled analgesia, consent for
Cardiorespiratory	Facilities for positive end expiratory pressure, blood gases and acid–base measurements hourly perioperatively
System assessments	
Cardiovascular right (left) heart	Prepare for hypo- and hypertension, consider intra-arterial catheter before induction
disease (carcinoid syndrome)	Echocardiogram, ECG
anaemia	Additional iron or transfusion
Respiratory	
bronchospasm (carcinoid)	Somatostatin analogues, steroids, ventilator characteristics
dyspnoea	Chest radiograph, echocardiography, blood gases
Liver/metabolism	
coagulation	Prothrombin time, thrombin time, activated partial thromboplastin time
biliary obstruction	Stent, fluids, maintain urine output with diuretics/dopamine
albumin/proteins	Nutritional assessment
glucose	Diabetic assessment and facilities for hourly blood glucose monitoring
portal hypertension	Expect increased blood loss
Renal/fluids	Normalize electrolytes, catheterize
Risk assessment	Explain risks, record in patient's notes
Intensive care	Booked admission
Medications	Prophylaxis: antithrombosis (after epidural), antibiotics Cautions in carcinoid sedatives, drugs releasing histamine, e.g morphine, thiopental, atracurium)

fluid abnormalities and hypovolaemia, maximizing and quantifying cardiac and respiratory function with electrocardiography, echocardiography, lung function tests and chest radiography, assessing liver function and clotting abnormalities (particularly if there are liver metastases) and minimizing any medical complication. Surgical assessment should have defined the type of endocrine dysfunction and the site of the tumour and predicted the magnitude of the surgical intervention and the need for prophylactic immunization before splenectomy.[53]

Major cardiovascular and respiratory crises are to be expected if the neuroendocrine tumours are functional. These may be precipitated by induction of anaesthesia, surgical manipulations or histamine-releasing drugs. In anticipation of such events, anaesthetic preparation includes preoperative medication with anxiolytic and antihistamine drugs and direct monitoring of arterial and central venous pressures before induction. Large-bore infusion sets should be available for administering warmed fluids and blood. A ventilation and breathing system which can accommodate high inflation pressures is also needed. The choice of anaesthetic and other drugs should be based on a consideration of the possible medical and surgical problems. The aim is to maintain cardiovascular stability and not to induce bronchospasm. Hence, drugs which are known to release histamine, serotonin or produce a catecholamine response, such as ketamine,[8] should be used with caution. For example, morphine can release histamine and is relatively contraindicated during but not after surgery when the tumour has been removed. Fentanyl is a short-acting alternative. Catecholamines, such as epinephrine, can release serotonin and kallikrein, which activates bradykinins. Theoretically, they should be avoided as vasopressors. Angiotensin is an alternative agent and can be given by infusion. However, the demand to exclude the use of epinephrine in carcinoid syndrome was based on experience before prophylaxis with somatostatin analogues and it has been used with effect as an inotropic agent during laparotomy and after cardiac surgery.[14 27]

A review of anaesthetic drugs for carcinoid syndrome has suggested that the hypertensive response to intubation should be prevented by using a short-acting opioid and etomidate or propofol.[47] Succinylcholine has been used safely for rapid sequence induction although hormone release theoretically could be stimulated by fasciculations increasing intra-abdominal pressure. Non-depolarizing neuromuscular blocking drugs should be selected on the basis of their lack of histamine release and ease of reversal. Vecuronium is the drug of choice, although in hepatic failure, atracurium should be considered. Agents for maintenance of anaesthesia primarily should be non-hepatoxic and cardiostable. In addition, where high concentrations of serotonin can cause drowsiness, agents with a short elimination time should be considered for safe postoperative recovery.[28] The choice of regional anaesthesia, particularly in carcinoid syndrome, is controversial because treatment of hypotension with catecholamines is contraindicated.[17] However, epidural nerve blocks using incremental or infusions of local anaesthetics without epinephrine have been administered effectively in a number of patients. They provide good pain relief to reduce the stress response and allow mobilization.[30, 47]

Blood loss during surgery depends on specific pathology. For example, carcinoid tumours induce an intense mesenteric reaction which may not have a focal point of bleeding; metastatic involvement of major vessels, such as the hepatic and portal vessels, can lead to a blood loss of 1–2 litres min^{-1}; the large incision will ooze blood over time and if portal hypertension is present blood loss occurs from the time of skin incision. These problems can be compounded if there are coagulation abnormalities. Average blood loss is 2 litres.[50] Blood loss can be assessed by weighing swabs and suction volume can but often this is not accurate because of fluid losses. A urinary catheter and half-hourly measures of urine output supported by blood gas, acid base and haemoglobin concentration measurements at hourly intervals provide the more detailed information required to make decisions on the amount of non-acute continuing bleeding. Adequate amounts of cross-matched blood with facilities to infuse and maintain blood volume and renal blood flow even in cardiovascularly compromised patients are basic requirements which can be supplemented by indirect measures of cardiac function, such as an oesophageal Doppler probe or transoesophageal echocardiography.

If therapies to reduce or antagonize hormone secretions have been administered perioperatively, slow withdrawal with close monitoring is advised.[46] Postoperative complications are common, and range from minor morbidity to death. A recent surgical review[37] reports a 3% hospital mortality. At operation, haemorrhage has been the major cause of death, especially in the elderly where cardiovascular and hepatic reserve is limited. After surgery, generalized or localized infections, for example intra-abdominal or pulmonary infections, can lead to septicaemia. Sepsis is common and poor nutrition and cachexia predispose to it. Thus nutritional assessment and treatment should be prioritized preoperatively and prophylactic antibiotics given perioperatively. Postoperatively, the appropriate antibiotic should be sought for any specific infection.

Conclusions

The well-defined clinical syndromes associated with hormone hypersecretion are Zollinger–Ellison syndrome from duodenal gastrinomas and carcinoid syndrome. Somatostatin analogues that inhibit hormone release have dramatically improved medical and surgical management but have long-term side-effects. Future development of drugs such as calcium channel blockers which act specifically on gastrointestinal tissues may broaden therapeutic choices in hypersecretion syndromes. Genetic predisposition has identified MEN1 with gastrinoma and MEN2 with somatostatin cell tumours. The multidisciplinary care from surgeons, endocrinologists, gastroenterologists, anaesthetists, radiologists, pathologists and geneticists necessitates an agreed management plan in a tertiary centre because of the rare and varied nature of the disorders. Surgery is the only approach that can achieve a definitive cure. The role of the anaesthetist in preoperative preparation, maintenance of perioperative homeostasis and postoperative high dependency or intensive care is one of the main factors in securing a good prognosis. Future progress in anaesthesia and intensive care management to secure this prognosis requires a prospective multicentre clinical study to establish evidence-based guidelines.

References

1 Batchelor AM, Conacher ID. Anaphylactoid or carcinoid? *Br J Anaesth* 1992; **69**: 325–7

2 Bieligk S, Jaffe BM Islet cell tumors of the pancreas. *Surg Clin N Am* 1995, **75**: 1025–40

3 Capella C, Heitz PU, Hofler H, Solcia E, Kloppel G. Revised classification of neuroendocrine tumours of the lungs, pancreas and gut. *Virchows Arch Pathol Anat Histopathol* 1995; **425**: 547–60

4 Chari P, Pandit SK, Kataria RN, Singh H, Baheti DK, Wig J. Anaesthetic management of insulinoma. *Anaesthesia* 1977; **32**. 261–4

5 Cheslyn Curtis S, Sitaram V, Williamson RC. Management of non-functioning neuroendocrine tumours of the pancreas. *Br J Surg* 1993; **80**: 625–7

6 Connolly HM, Nashimura RA, Smith HC, Pellikka PA, Mullany CJ, Kvols LK. Outcome of cardiac surgery for carcinoid heart disease. *J Am Coll Cardiol* 1995; **25**: 410–16

7 Decker RA, Peacock ML, Borst MT, Sweet DD, Thompsin NW. Progress in genetic screening of multiple endocrine neoplasia type 2A: Is calcitonin testing obsolete? *Surgery* 1995; **118**: 257–64

8 Eisenkraft JB, Dimich I, Miller R. Ketamine–diazepam anaesthesia in a patient with carcinoid syndrome. *Anaesthesia* 1981; **36**: 881–5

9 Feldman JM, O'Dorisio TM. Role of neuropeptides and serotonin in the diagnosis of carcinoid tumors. *Am J Med* 1986; **81**: 41–8

10 Fuller RW, Maxwell DL, Dixon CM, McGregor GP, Barnes VF, Bloom SR, Barnes PJ. Effect of substance P on cardiovascular and respiratory function in subjects. *J Appl Physiol* 1987; **62** 1473–9

11 Gilbey SG, Turner RC, Wynick D, Bloom SR. Endocrine tumours of the pancreas. In Khan CR, Weir GC, eds. *Diabetes mellitus*. Philadelphia: Lea & Febiger, 1994: 1000–1022

12 Goldstone AP, Scott-Combes DM, Lynn JA. Surgical management of gastrointestinal endocrine tumours. *Baillière Clin Gastroenterol* 1996; **10**: 707–36

13 Grant CS. Insulinoma. *Baillière Clin Gastroenterol* 1996; **10**: 645–71

14 Hamid SK, Harris DNF. Hypotension following valve replacment surgery in carcinoid heart disease. *Anaesthesia* 1992; **47**: 490–92

15 Houghton K, Carter JA. Peri-operative management of carcinoid syndrome using ketanserin. *Anaesthesia* 1986; **41**: 596–9

16 Hughes EW, Hodkinson BP. Carcinoid syndrome: the combined use of ketanserin and octreotide in the management of an acute crisis during anaesthesia. *Anaesth Intensive Care* 1989; **17**: 367–70

17 Hutton P, Cooper G. *Guidelines in Clinical Anaesthesia.* London: Blackwell Scientific, 1985: 209–47

18 Imamura M. Progress in the field of pancreatic endocrine tumors in Japan. *Pancreas* 1998; **16**: 379–84

19 Jacobsen MB, Nitter-Hauge S, Bryde PE, Hanssen LE. Cardiac manifestations in mid gut carcinoid. *Eur Heart J* 1995; **16**: 263–8

20 Jensen RT. Gastrinoma. *Baillière Clin Gastroenterol* 1996; **10**: 603–43

21 Kannan S, Puri GD, Chari P. Anesthetic management of a patient with an obstructing carinal carcinoid for tumor excision and pneumonectomy. *J Cardiothorac Vasc Anesth* 1998; **12**: 192–4

22 Keens SJ, Desmond MJ, Utting JE. Carcinoid syndrome with myasthenia gravis. An unusual and interesting case. *Anaesthesia* 1986; **41**: 404–7

23 Kulke MH, Mayer RJ. Carcinoid tumors. *New Engl J Med* 1999; **340**: 858–68

24 Lange JR, Steinberg SM, Doherty GM, Langstein HN, White DE, Shawker TH, Eastman RC, Jensen RT, Norton JA. A randomised, prospective trial of postoperative somatostatin analogue in patients with neuroendocrine tumors of the pancreas. *Surgery* 1992; **112**: 1033–7

25 Le Roith D. Tumor-induced hypoglycemia. *New Engl J Med* 1999; **341**: 757–8

26 Lipmann M, Cleveland B. Anesthetic management of a carcinoid patient undergoing tricuspid valve replacement. *Anesth Analges* 1973; **52**: 768–71

27 Marsh HM, Martin JK, Kvols LK, Gracey DR, Warner MA, Warner ME, Moertel CG. Carcinoid crisis during anesthesia: successful treatment with a somatostatin analogue. *Anesthesiology* 1987; **66**: 89–91

28 Mason RA, Steane PA. Carcinoid syndrome: its relevance to the anaesthetist. *Anaesthesia* 1976; **31**: 228–42

29 Matsumoto M, Sakai H. Sevoflurane anesthesia for a patient with insulinoma. *Masui* 1992; **41**: 446–9

30 Monteith K, Roaseg OP. Epidural anaesthesia for transurethral resection of the prostate in a patient with carcinoid syndrome *Can J Anaesth* 1990; **37**: 349–52

31 Muir JJ, Endress SM, Offord K, van-Heerden JA, Tinker JH. Glucose management in patients undergoing operation for insulinoma removal. *Anesthesiology* 1983; **59**: 371–5

32 Murphy DM, Lochhart CH, Burrington JD. Anaesthetic considerations in bronchial adenoma. *Can Anaesth Soc J* 1975; **22**: 710–4

33 Norheim I, Theodorsson-Norheim E, Brodin E, Oberg K. Tachykinins in carcinoid tumours: their use as a tumour marker and possible role in the carcinoid flush. *J Clin Endocrinol Metab* 1986; **63**: 605–12

34 Norton JA, Fraker DL, Alexander R, Venzon DJ, Doppman JL, Serrano J *et al.* *Surgery* to cure the Zollinger–Ellison syndrome. *New Engl J Med* 1999; **341**: 635–44

35 Padfield NL. Carcinoid syndrome: comparison of pre-treatment regimes in the same patient. *Ann Roy Coll Surg* 1987; **69**: 16–17

36 Proye CAG, Nguyen HH. Current perspectives in the surgery of multiple endocrine neoplasias. *Austral New Zeal J Surg* 1999; **69**: 106–16

37 Phan GQ, Yeo CJ, Hruban RH, Lillemoe KD, Pitt HA, Cameron JL. Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: review of 125 patients *J Gastrointest Surg* 1998; **2**: 472–82

38 Roy RC, Carter RF, Wright PD. Somatostatin, anaesthesia and the carcinoid syndrome. Peri-operative administration of a somatostatin analogue to suppress tumour activity. *Anaesthesia* 1987; **42**: 627–32

39 Ridker PM, Chertow GM, Karlson EW, Neish AS, Schoen FJ. Bioprosthetic tricuspid valve stenosis associated with extensive plaque deposition in carcinoid heart disease. *Am Heart J* 1991; **121**: 1835–8

40 Sato Y, Onozawa H, Fujiwara C, Kamide M, Yanifuji Y, Amaki Y. Propofol anaesthesia for a patient with insulinoma. *Masui* 1998; **47**: 738–41

41 Solares G, Blanco E, Pulgar S, Diago C, Ramos F. Carcinoid syndrome and intravenous cyproheptadine. *Anaesthesia* 1987; **42**: 989–92

42 Tiensuu-Janson EM, Oberg KE. Carcinoid tumours. *Baillière Clin Gastroenterol* 1996; **10**: 589–601

43 Thorson Å, Biorck G, Bjorkman G, Waldenström J. Malignant carcinoid of the small intestine with metastases to the liver, valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and an unusual type of cyanosis: a clinical and pathological syndrome. *Am Heart J* 1954; **47**: 795–817

44 Tulassay Z. Somatostatin and the gastrointestinal tract. *Scand J Gastroenterol* 1998; **33**: 115–21

45 Ulbrecht JS, Schmeltz R, Aarons JH, Greene DA. Insulinoma in a 94-year old woman: long term therapy with verapamil. *Diabet Care* 1986; **9**: 186–8

46 Vaughan DJA, Brunner MD. Anesthesia for patients with carcinoid syndrome. *Int Anesthesiol Clin* 1997; **35**: 129–42

47 Veall GRQ, Peacock JE, Bax NDS, Reilly CS. Review of the anaesthetic management of 21 patients undergoing laparotomy for carcinoid syndrome. *Br J Anaesth* 1994; **72**: 335–41

48 Waltenberger J, Lundin L, Oberg K, Wilander E. Involvement of transforming growth factor-β in the formation of fibrotic lesions in carcinoid heart disease. *Am J Pathol* 1993; **142**: 71–8

49 Whipple AO, Franz VK. Adenoma of islet cells with hyperinsulinaemia. *Am Surg* 1935; **101**: 1299–335

50 Whitwam JG. APUD cells and the apudomas. A concept relevant to anaesthesia and endocrinology. *Anaesthesia* 1977; **32**: 879–88

51 Wilde MI, Markham A. Ondansetron. A review of its pharmacology and preliminary clinical findings in novel applications. *Drugs* 1996; **52**. 773–94

52 Watanapa P, Williamson RC. Resection of the pancreatic head with or without gastrectomy. *World J Surg* 1995; **19**: 403–9

53 Working Party of the British Committee for Standards in Haematology. Clinical Haematology Task Force. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *Br Med J* 1996; **312**: 430–34

54 Wynick D, Williams SJ, Bloom SR. Symptomatic secondary hormone syndromes in patients with established malignant pancreatic endocrine tumours. *New Engl J Med* 1988; **319**: 605–7

55 Zonta F, Dondi G, Barbieri A, Grana E. Study of the negative inotropic action of somatostatin. *Arch Int Pharmacodyn Ther* 1989; **300**: 149–58

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Insulin: understanding its action in health and disease

P. Sonksen[1]* and J. Sonksen[2]

[1]GKT Medical School, King's College London, St Thomas' Hospital, London SE1 7EH, UK. [2]Russells Hall Hospital, Dudley, West Midlands DY1 2HQ, UK

*Corresponding author

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> *The results of pancreas extirpation and pancreas grafting are best explained by supposing that the islet tissue produce an Autacoid which passes into the blood stream and effects carbohydrate metabolism and carbohydrate storage in such a manner that there is no undue accumulation of glucose in the blood. Provisionally it will be convenient to refer to this hypothetical substance as insuline.*
>
> Sir Edward Schafer, *The Endocrine Organs* (1916)

Historical background

Sir Edward Schafer, who was Professor of Physiology in Edinburgh, appears to have named insulin and described its actions. He did so in a book, *The Endocrine Organs*, based on a lecture series he gave in California in 1913. In this book, published in 1916,[5] he gave the hypothetical substance a name that stuck; what is more, with remarkable vision, he described its likely formation from activation of an inert precursor:

> *It must however be stated that it has yet to be determined whether the active substance is produced as such in the pancreas or whether it exists there as pro-insuline which becomes elsewhere converted into the active autacoid.*

Insulin was discovered 8 yr later by Banting and Best in 1921. The first patient was treated a year later in 1922 and pro-insulin was discovered (and re-named) more than 50 yr later by George Steiner of the University of Chicago in 1967.

Schafer deliberately avoided using the word 'hormone' and used his preferred terms 'autacoid' and 'chalone'. This was as a result of long-standing academic rivalry with his contemporaries Professors Baylis and Starling at University College, London. They had previously described secretin as the first hormone to be isolated and characterized. They had coined the term 'hormones' to describe the class of substance produced in one part of the body and acting elsewhere. Schafer preferred his own terms, which were based on terms used at the time to describe actions of drugs, 'autacoid' being a substance with excitatory action and 'chalone' one with inhibitory action.

Schafer went on to describe how 'insuline' had both excitatory and inhibitory actions. His description of how he thought the hypothetical substance 'insuline' acted in the body is remarkable because the passage of time has shown him to be correct almost word for word. Things have been confused, however, by a 20 yr 'black age' of endocrinology (between approximately 1960 and 1980), where leading scientists—through extrapolating beyond their new discoveries—confused scientific thinking and teaching. They formulated new hypotheses based for the first time on hard scientific evidence but they got it badly wrong through extrapolating (incorrectly) from *in vitro* experimental data in rat tissues to *in vivo* metabolism in humans.

The effects of this 'black age' are still with us because these incorrect hypotheses have, with the passage of time, been turned into dogma and become cast into 'tablets of stone' in undergraduate textbooks. They are also carried forward into postgraduate teaching. For example, even in well respected texts it is still common to find statements such as 'The basic action of insulin is to facilitate glucose entry into cells, primarily skeletal muscle and hepatocytes.'[1]

Purpose of this review

The main thrust of this article is to set the record straight, provide up-to-date information about current understanding and confirm that Schafer, through careful thought and despite lack of experimental data, was correct. We also hope to show how this 'new' concept of insulin action affects the modern management of diabetes during surgery and in the intensive care unit.

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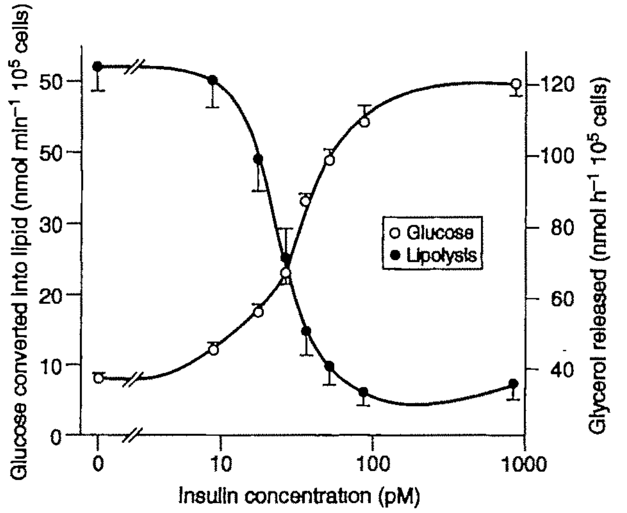

Fig 1 Insulin action on isolated rat adipocytes Insulin simultaneously stimulates lipogenesis from glucose and inhibits lipolysis. Both mechanisms are mediated by the same receptor. The data illustrate what Schafer referred to as the 'autacoid' (excitatory) action, i e stimulation of lipogenesis, and the 'chalonic' (inhibitory) action, i e inhibition of lipolysis, both of which are integral to the hormone and mediated by the same receptor It is the 'chalonic' action which has most relevance to human physiology and the use of insulin therapeutically.

Insulin as an autacoid and chalone

As Schafer hypothesized, insulin has two classes of action: (i) excitatory (autacoid), for example stimulating glucose uptake and lipid synthesis; and (ii) inhibitory (chalone), for example inhibiting lipolysis, proteolysis, glycogenolysis, gluconeogenesis and ketogenesis. These dual actions are illustrated in Fig. 1, where insulin's well recognized action in stimulating lipogenesis from glucose (in rat adipocytes) is illustrated.[6] What perhaps is less well known is insulin's simultaneous inhibitory action on lipolysis. It is quite clear from Fig. 1 that both these actions occur simultaneously over the same concentration range. They are both mediated through the same cell membrane receptor. These actions of insulin *in vitro* were discovered in the late 1950s when it was also shown that insulin stimulated glucose uptake by rat muscle. It was extrapolation of this last observation in rat muscle to explain the pathophysiology of diabetes that was erroneous. The consequence of this error was the (fallacious) concept of insulin being 'required' for glucose entry into cells rather than just accelerating glucose uptake. The hyperglycaemia of diabetes was interpreted as a 'damming back' of glucose in the blood stream as a consequence of a lack of insulin. This became established teaching and, although the concept was shown to be erroneous in the mid-1970s, the teaching has not changed. Consequently, therapy has been based on a flawed concept.

It is now well established that what Schafer called insulin's 'chalonic' (or inhibitory) actions are the physiologically more important. Indeed, its autacoid (excitatory) action has recently been shown to be, on the whole, physiologically unimportant. Insulin's excitatory actions are effectively abolished in the genetically engineered muscle insulin receptor knock-out (MIRKO) mouse because they have a complete lack of the insulin-sensitive glucose transport protein, Glut 4, in muscle, so insulin has no stimulatory effect on glucose uptake. Fascinatingly, this is of little or no consequence to the animal that does not have fasting hyperglycaemia or diabetes.

The nature of fasting hyperglycaemia

The key question is: is the fasting hyperglycaemia of diabetes due to overproduction of glucose by the liver or underutilization of glucose by peripheral tissues?

When this question was posed to participants of the Royal College of Anaesthetists' Basic Science Course in 1998 and 1999, a show of hands revealed virtually unanimous support for the second alternative, with only one or two hands in favour of the correct answer (overproduction of glucose by the liver). This is a typical response, seen from the overwhelming majority of both undergraduate and postgraduate audiences in the UK and the rest of the world. It is important to have the right understanding if insulin is to be used appropriately and to maximum benefit. This may perhaps seem a trivial or pedantic point but it is not. Correct understanding of what goes wrong with metabolism in the face of insulin deficiency is essential in the understanding and execution of logical and safe forms of treatment.

Fasting normoglycaemia

Consider a person with a normal fasting blood glucose concentration of 5 mmol litre^{-1}. The stable fasting blood glucose concentration conceals an underlying dynamic steady state where the glucose that is continuously being cleared from the circulation for metabolism is exactly matched by new glucose being added by the liver. This dynamic steady state is normally controlled very tightly by insulin. Glucose input into the circulation (rate of appearance, or R_a) is normally approximately 12 μmol kg^{-1} min^{-1} (2 mg kg^{-1} min^{-1}), and in the fasting state is exclusively from the liver, exactly matches glucose disposal in peripheral tissues (rate of disappearance, or R_d). The main contributors to glucose disappearance (or clearance) in the fasting, resting state are the brain (~50%), lean tissues (~30%), adipose tissue (~10%) and red blood cells (~10%). This is illustrated in Fig. 2.

Fasting hyperglycaemia

Next consider a hypothetical patient with type 2 diabetes presenting for elective surgery. Fasting blood glucose in this case is, let us say, 12 mmol litre^{-1} (which remains quite steady with short-term fasting). This again reflects a balance between hepatic glucose production on one hand and

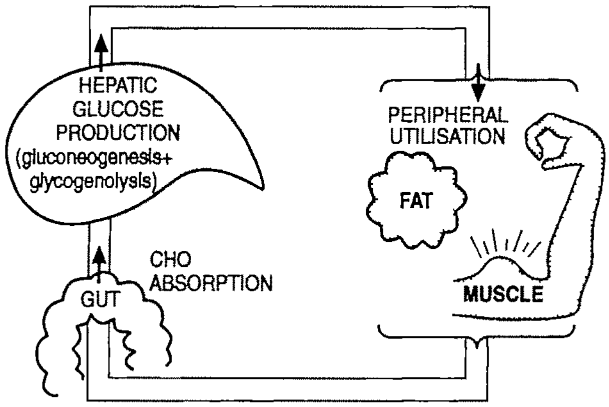

Fig 2 A cartoon illustrating the dynamic steady state that exists between glucose production and utilization. The brain is not shown. Blood glucose concentration is tightly controlled during fasting and feeding through mechanisms balancing exactly the supply and demand of energy substrate. Insulin is the prime controller of this process. When fasting hyperglycaemia develops, as in diabetes mellitus, it could result from either over-production of glucose, through excess glycogenolysis and gluconeogenesis, or a failure of adequate glucose uptake in the peripheral tissues (including the brain). Most people think that hyperglycaemia reflects a reduction in glucose uptake as a result of insulin deficiency This is not true

peripheral glucose utilization on the other. In this case, however, because blood glucose concentration is above the renal threshold for glucose, the rate of glucose disposal (R_d) is a combination of the rate of tissue utilization (R_{ut}) and the rate of urinary loss (R_u). The two always balance to produce a steady state because glycosuria (R_u) increases rapidly and linearly with the increase in blood glucose concentration once the renal threshold has been crossed. Thus, R_d increases until it matches R_a, when a new steady state is achieved. For this reason it is the extent of the hepatic overproduction of glucose (R_a) that sets the degree of fasting hyperglycaemia; the higher the fasting hyperglycaemia, the higher R_a and the more severe the diabetes.

It is now easy to measure R_a and R_d experimentally and thus answer the question posed at the beginning of this section. Initially, this was done by injecting radioactive (^{14}C- or ^{3}H-labelled) glucose and measuring the rate at which it was diluted with unlabelled glucose from the liver (the concentration of glucose remains constant but the concentration of ^{14}C- or ^{3}H-labelled glucose falls exponentially with time). It is quite easy to calculate accurately the actual rates of glucose production and utilization from this isotope dilution curve. It is now possible to make these measurements without the need for radioactive tracers, using instead glucose labelled with a natural stable isotope of carbon (^{13}C), thus avoiding any radiation hazard and even allowing research on diabetes in pregnancy.

In the fasting state, virtually all glucose R_a comes from the liver, from a combination of glycogenolysis and gluconeogenesis. When hepatic glycogen stores are plentiful, most glucose comes from glycogenolysis, but as the hepatic glycogen stores become depleted, more comes from gluconeogenesis. After 24 h of starvation, hepatic glycogen stores are completely exhausted and all glucose production comes from gluconeogenesis (muscle glycogen cannot contribute to blood glucose as there is no glucose-6-phosphatase in muscle and glucose transporters cannot transport glucose 6-phosphate out of muscle. The kidney may, on occasions, make a minor contribution to gluconeogenesis.)

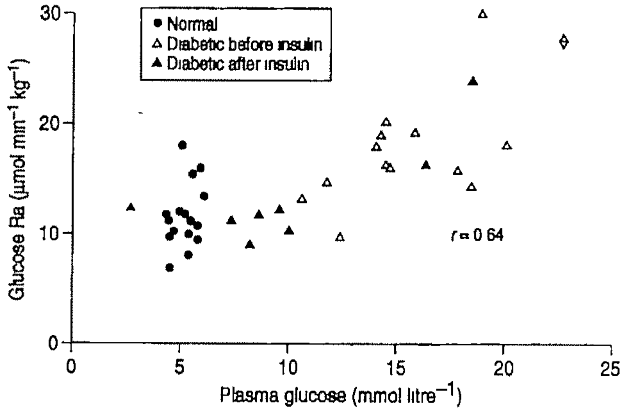

Fig 3 Fasting plasma glucose and isotope-determined glucose turnover rate in a group of newly diagnosed patients with diabetes studied before and after starting insulin compared with non-diabetic controls. In the newly diagnosed patients, glucose turnover (rate of production and rate of utilization) is elevated in proportion to fasting blood glucose This shows that the fasting hyperglycaemia of diabetes results from hepatic over-production of glucose alone, since peripheral glucose utilization is increased despite the lack of insulin Insulin treatment reduces glucose concentration through inhibiting hepatic glucose production Under these conditions glucose utilization decreases, thus insulin administration ***reduces*** glucose utilization This indicates that the plasma glucose concentration, rather than plasma insulin, is the prime determinant of glucose uptake There are clearly sufficient glucose transporters present, even in the newly diagnosed diabetic state, to ensure adequate glucose metabolism Thus insulin regulates glucose production more than glucose utilization.

Experimental observations in people with newly diagnosed diabetes or in insulin-withdrawn patients with both type 1 and type 2 diabetes have shown that there is a strongly positive relationship between the fasting blood glucose concentration and the rate of hepatic glucose production (R_a). This was first shown in the early 1970s in animals and in the mid-1970s in humans.[3] It is illustrated in Fig. 3.

The normal fasting–feeding cycle ('energy metabolism')

The role of glucose

Normally, fasting blood glucose concentration is very tightly controlled by insulin secretion at a mean of about 5 mmol litre^{-1}. There is a much wider range of glucose production rates (R_a) and glucose utilization rates (R_d)

between normal individuals than there is in fasting blood glucose concentrations (see Fig. 3). This is because of the feedback control loop between blood glucose concentration and insulin secretion. The rates of fasting hepatic glucose production and glucose utilization (R_a and R_d) in each individual remain exactly matched and relatively constant over days, months and even years and are probably largely genetically determined.

The fact that fasting blood glucose concentration remains constant over minutes and hours reflects an exact balance between input and output of glucose from the circulation (R_a=R_d). In non-diabetics, all of R_d is going to metabolism, so the hormonal control mechanisms are geared to releasing sufficient glucose to match the body's need. This is a very basic and robust process, so that a healthy individual can survive a remarkably long time without eating, so long as they have access to water. Hypoglycaemia is not a feature of prolonged starvation; there are powerful 'survival' values in being able to maintain brain function during prolonged famine. Since hepatic glycogen stores are depleted within 24 h of fasting, blood glucose concentrations are maintained thereafter entirely through gluconeogenesis. Gluconeogenesis is mainly dependent on protein breakdown (a small amount comes from the glycerol released during lipolysis) and it thus results in protein wasting. It is the effects of protein malnutrition that lead to the eventual lack of ability to cough properly and keep the airways clear, in turn leading to pneumonia and death during prolonged starvation; hypoglycaemia does not occur. During fasting, mobilization of fat and the consumption of fat and ketones by some tissues as 'alternative substrates' ensures that protein loss is minimized and used to provide glucose for tissues, such as the brain, that cannot survive without it.

With normal feeding, digestion of carbohydrates leads to a rise in blood glucose, which normally triggers a brisk insulin response of sufficient magnitude to control blood glucose concentration very tightly in the 4–10 mmol litre^{-1} range. The *average* peak plasma insulin response to a high carbohydrate meal in a group of normal healthy slim individuals rises 10-fold from a mean fasting value of 5 mU litre^{-1} to a peak of about 50 mU litre^{-1}. The *range* of insulin response in this group is enormous, however, with peak values ranging between 15 and 250 mU litre^{-1} while glucose values are no different between individuals. This reflects a genetically determined variation in insulin sensitivity between individuals.

Some glucose is stored in muscle as glycogen. This compartment of stored glucose is entirely for the 'local use' of muscle and is integral to the 'flight or fight' survival mechanism that has resulted in humans being the dominant creatures on earth. Muscle lacks a certain phosphorylase enzyme that removes the phosphate group from glucose 6-phosphate and as a result, free intracellular glucose is not produced by glycogenolysis in muscle (unlike the liver) and muscle cannot therefore 'export' glucose into the circulation. Muscle glycogen allows a sudden burst of fuel (through anaerobic metabolism of glycogen to glucose to lactate) which allows muscle to undertake an immediate sudden burst of extreme activity on locally available energy stores before blood flow builds up to carry the lactate away and bring other energy fuels to sustain more prolonged exercise. Thus the fuel used by muscle progresses from local glycogen (sprint) to glucose and fatty acids brought via the circulation (middle distance) to predominantly fat (marathon).

The roles of fat and protein

The other major fuel required for 'energy metabolism' is fat. Stored fat is in the form of triglyceride and contains enormous amounts of stored energy. Fat contains 9 kcal g^{-1} stored energy while glycogen contains only 2 kcal g^{-1} because there is water of hydration in glycogen in both muscle and the liver. This means that glycogen stores are heavy and of limited value to mobile creatures like us. They are there for short-term needs but, when food is scarce, a transition occurs to substitution of fat in all tissues that can metabolize it. Hepatic glycogen stores are soon lost during fasting, and gluconeogenesis—mainly from protein—is then required to maintain glucose supplies to the central nervous system. Since protein stores are also limited and critical to survival, the substitution of fat wherever possible is of great value. The enormous amount of energy stored in fat is liberated through lipolysis where triglyceride is hydrolysed to its constituents, glycerol and non-esterified fatty acids (NEFA; also known as free fatty acids (FFA)). Fat is able to substitute for glucose as an energy substrate in many but not all tissues. In muscle, there is no real preference for glucose or NEFA and the tissue can and does readily change from one to the other. The brain and other neural tissues have an obligatory requirement for glucose and cannot survive without it; however, they can substitute ketones (but not NEFA) for some, but not all, of their energy needs.

Protein is used mainly for structural processes but is continuously being synthesized and broken down. When food is short and glycogen stores are depleted, protein becomes the major source of gluconeogenic precursors via the 'glucogenic' amino acids released during proteolysis. Proteolysis is inhibited by insulin (another of Schafer's 'chalonic' actions) and, in states of relative insulin lack such as prolonged fasting, insulin concentrations fall low enough to allow release of sufficient gluconeogenic amino acids to maintain blood glucose in the normal range. The price for this is a gradual but progressive loss of structural protein. As stated earlier, it is this that determines survival during prolonged fasts.

What goes wrong in diabetes?

Fasting hyperglycaemia is the hallmark of diabetes. In the very early stages, so-called impaired glucose tolerance (IGT), fasting blood glucose concentration is normal and only the response to a glucose challenge is impaired. In

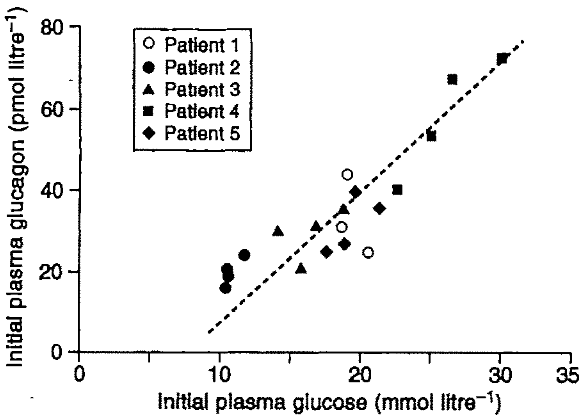

Fig 4 Fasting plasma glucose concentration is determined not only by fasting plasma insulin but also by glucagon. These data were obtained from a group of five type 1 diabetic patients who withheld insulin for 24 h on four separate occasions There was a very close correlation between fasting blood glucose and plasma glucagon, also, on each occasion the same individual achieved a remarkably similar fasting plasma glucose and glucagon concentration.

symptomatic diabetes, fasting hyperglycaemia is always present and random blood glucose concentrations are always in excess of 11 mmol litre^{-1}, often considerably so. For the classical symptoms of thirst, polyuria and weight loss to occur, there must be heavy glycosuria. By and large, the severity of the metabolic disturbance is reflected accurately in the degree of elevation of the fasting blood glucose concentration (which reflects the magnitude of the hepatic overproduction of glucose). This is illustrated in Fig. 3.

Even when the fasting blood glucose concentration is as high as 20 mmol litre^{-1}, it remains constant over several hours of fasting. During this time, a dynamic steady state exists when glucose production matches glucose disappearance from the bloodstream exactly. The magnitude of the hyperglycaemia is determined by the absolute rate of hepatic glucose production (Fig. 3) and this in turn is determined by the extent of, on one hand, the insulin deficiency and, on the other hand, the magnitude of the glucagon rise in response to insulin deficiency. This is another key point. In patients with diabetes mellitus secondary to pancreatectomy, where glucagon concentrations are low, fasting hyperglycaemia is modest. In type 1 diabetes, glucagon production is unimpaired and, in the face of insulin deficiency, plasma concentrations rise rapidly to high concentrations. In a group of insulin-withdrawn type 1 patients, where no insulin had been given for 24 h, fasting plasma glucose (and hence hepatic glucose production) correlated remarkably closely with fasting plasma glucagon[2] as shown in Fig. 4.

Glucose uptake into cells is usually normal and often high in untreated diabetes

Since there is a dynamic steady state during short-term fasting, glucose production exactly matches glucose clearance from the plasma. In the face of hyperglycaemia, glucose clearance represents both tissue glucose metabolism and urinary glucose loss. By collecting urine and measuring the losses directly, tissue glucose metabolism can be calculated readily. Such calculations show that, in the face of hyperglycaemia, tissue glucose uptake is usually increased above normal even when insulin deficiency is severe. This cannot be reconciled with the concept that insulin is required for glucose uptake by insulin-sensitive tissues. Indeed it proves beyond question that insulin is *not* required. We now know the detailed mechanisms involved and can explain this. Glucose uptake by all cells is by means of a specific transport protein (glucose transporter) of which at least six isomers (Glut 1 to Glut 6) are known. Glucose is a highly polar substance, being freely soluble in water but insoluble in fat. It cannot enter cells except through the specific transport system utilizing Glut 1–6. Glut 4 is the transport protein present in muscle and adipose tissue, which is known to be 'insulin sensitive'. This means that, in addition to the transporters resident in the cell membrane at any given moment, there is a pool of glucose transporter molecules in the cytoplasm of the cell which can be recruited in response to a rise in plasma insulin, to join those already in the cell membrane in the fasting state. We now know, from experiments like those illustrated in Fig. 3, that even in the fasting state or in a state of absolute insulin deficiency, there are sufficient glucose transporters already in place in the cell membrane to allow glucose uptake to exceed that of a normal individual when the gradient of glucose concentration across the cell membrane is sufficiently high.

This 'mass action' effect accounts for the observations which show unequivocally that tissue glucose uptake can exceed normal even in the face of severe insulin deficiency such as occurs in uncontrolled diabetes mellitus.

Ketosis inhibits glucose uptake in many tissues and thus can 'spare' structural protein

Glucose uptake is not, however, increased in all diabetic patients with hyperglycaemia. When significant ketosis occurs, this can inhibit glucose metabolism in cells, because the ketone bodies (3-hydroxybutyrate, acetoacetate and acetone) are freely soluble in both water and fat and diffuse across the cell membrane in direct proportion to their concentration in plasma. They are metabolized intracellularly to acetoacetate, which enters the Krebs' cycle and becomes oxidized to carbon dioxide and water. When ketone concentrations in the plasma are high (above about 15 mmol litre^{-1}), their metabolism can account for most of the energy needs of the Krebs' cycle. This results in a physiological 'damming back' of glycolysis from glucose. As a result, the concentration of the intermediate compounds in the glycolytic pathway increases until the tissue concentration of glucose 6-phosphate is so high that further phosphorylation of glucose that has been transported into

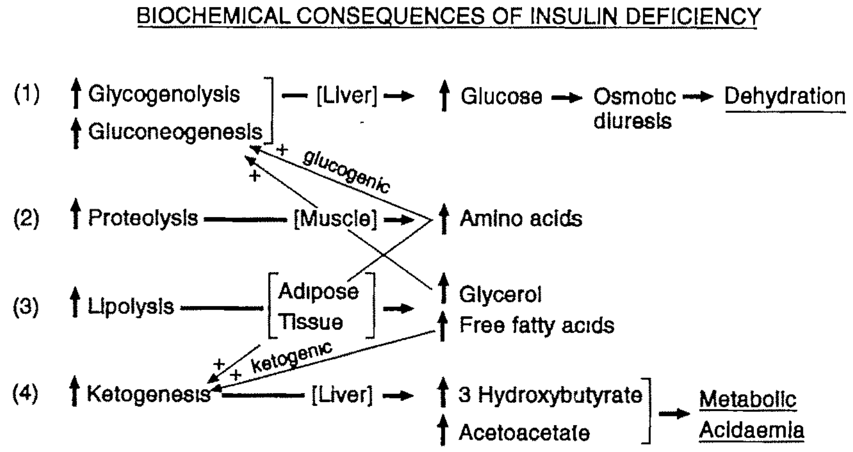
BIOCHEMICAL CONSEQUENCES OF INSULIN DEFICIENCY
(1) ↑ Glycogenolysis
↑ Gluconeogenesis
— [Liver] → ↑ Glucose → Osmotic diuresis → Dehydration
+
+ glucogenic
(2) ↑ Proteolysis — [Muscle] → ↑ Amino acids
(3) ↑ Lipolysis — [Adipose Tissue] → ↑ Glycerol
↑ Free fatty acids
+
+ ketogenic
(4) ↑ Ketogenesis — [Liver] → ↑ 3 Hydroxybutyrate
↑ Acetoacetate
→ Metabolic Acidaemia

Fig 5 The biochemical consequences of insulin deficiency are summarized in this illustration Insulin normally has a tonic inhibitory control (what Schafer termed 'chalonic' action) on the supply of energy substrates arising mainly from metabolism in the liver, muscle and adipose tissue. Normally insulin ensures sufficient release of appropriate substrate to allow humans to cope with the eventualities of life in a highly controlled manner. Once insulin deficiency develops this control is lost, and energy substrates are over-produced and flood the system The metabolic consequences result from the excess of substrates not (as is often misconceived) by a lack of energy substrate getting to the tissues

the cell becomes inhibited. Even when this stage is reached, glucose transport into the cell continues but, rather than being phosphorylated and passing down the glycolytic pathway and oxidized in the Krebs' cycle, glucose is transported back out of the cell ('futile cycling'). The glucose transporter is specific for glucose and cannot transport glucose 6-phosphate.

Thus glucose transport and uptake into cells are dependent on the degree of ketosis. In the face of extreme ketosis, such as that not uncommonly seen in type 1 diabetes, where concentrations rise to as high as 25 mmol litre^{-1}, glucose uptake can be reduced to almost zero in tissues, such as muscle, that can metabolize ketones as readily as glucose. Under these conditions, glucose uptake in brain and other neural tissues (which can metabolize limited amounts of ketones) is reduced but ketones can never substitute completely for glucose. Red blood cells, on the other hand, do not have nuclei or mitochondria, cannot metabolize ketones at all and rely entirely on glucose conversion to lactate for their energy needs.

Ketoacidosis in diabetes is an uncontrolled process where serious lack of insulin 'takes the brake off' lipolysis and ketogenesis. The result is severe ketosis, which can readily become ketoacidosis and can easily be fatal once ketoacids reach concentrations above 20 mmol litre^{-1} and compensatory mechanisms become exhausted.

Controlled ketosis occurs with prolonged fasting in non-diabetics. Insulin levels fall sufficiently to release enough NEFA and to activate the hepatic enzymes of ketogenesis sufficiently to allow ketoacids to reach concentrations of <7 mmol litre^{-1}. This is a 70-fold increase over their normal fasting concentration (around 0.1 mmol litre^{-1}) and sufficient to supply energy for those tissues able to substitute ketones for glucose. In muscle this is as high as 100%, in red blood cells it is 0 and in the central nervous system it can be as high as about 50%. Thus the need for glucose is reduced and structural protein is preserved.

Mechanisms leading to the development of diabetic ketoacidosis and hyperosmolar non-ketotic diabetic coma

Schafer's concept of insulin's main action being as a chalone has been shown to be correct. Thus insulin normally 'keeps the brakes on' a number of key metabolic processes including the supply of all 'fuels' needed for metabolism from glycogenolysis, gluconeogenesis, lipolysis, ketogenesis and proteolysis. In the presence of severe insulin deficiency, such as occurs in diabetic ketoacidosis, the 'brake' is removed and the net result is a sort of metabolic mayhem. In keeping with the basis of 'Murphy's law' (when one thing goes wrong, so does every thing else); insulin deficiency itself leads to over-secretion of the 'anti-insulin' hormones glucagon, cortisol, growth hormone and catecholamines. This in turn aggravates the metabolic effects of insulin lack. This is summarized in Fig. 5.

Glycogenolysis and gluconeogenesis are activated as a result of lack of insulin in the liver; the rates of these processes are further enhanced by over-production of hormones such as glucagon and cortisol, which stimulate these processes, particularly in the face of insulin deficiency. The net result is that the liver pours glucose into the circulation much more quickly than the tissues can metabolize it. This leads to a progressive increase in blood glucose concentration. When this exceeds the renal threshold, glycosuria develops and fasting blood glucose eventually reaches a dynamic steady state where over-production of glucose by the liver is matched by increase clearance through metabolism in the tissues (R_{ut}) and excretion in the urine (R_u). Under these steady-state conditions, $R_a=R_d=R_{ut}+R_u$.

Proteolysis is enhanced as a result of lack of insulin in muscle, providing a supply of glucogenic and ketogenic amino acids. The glucogenic amino acids (alanine, arginine, etc.) pass to the liver to fuel the furnace of gluconeogenesis. In addition, lack of insulin at the liver activates the enzymes of gluconeogenesis. The 'ketogenic' amino acids (leucine, isoleucine and valine) released from proteolysis contribute to the substrates for hepatic ketogenesis.

As a result of lack of insulin in adipose tissue, lipolysis proceeds at an accelerated rate and this is further enhanced by over-secretion of growth hormone and catecholamines. Stored triglyceride is hydrolysed to glycerol and NEFA. The glycerol passes to the liver and contributes significantly to gluconeogenesis while the NEFA are transported to the liver and provide the major substrate for ketogenesis. Plasma concentrations of NEFA rarely increase above 1.5 mmol litre^{-1} since NEFA are insoluble in water (highly non-polar) and rely on albumin binding for transport in the extracellular fluids. At 1.5 mmol litre^{-1}, all protein binding is saturated. NEFA are metabolized very quickly with a plasma half-life of 1–2 min, thus flux through the blood can be very high without the concentration rising above 1.5 mmol litre^{-1}.

As a result of insulin lack, the liver is also 'primed' for ketogenesis as insulin deficiency activates the appropriate enzymes of ketogenesis. With increased flux of NEFA substrate arriving at the liver from accelerated lipolysis, the net result is that the liver pours out ketoacids (3-hydroxybutyric and acetoacetic acids) into the blood stream, where R_a exceeds R_d, so their concentrations in the blood increase progressively. In this case, although ketones are excreted in the urine, there is no 'renal threshold' and unlike glucose the urinary losses are not very great and do not lead to the development of a new steady-state blood ketone concentration. The only significant loss of ketones from the circulation is, therefore, from metabolism. Since ketones are freely soluble in water and lipid, they enter all cells at high concentrations and are metabolized in preference to glucose in cells capable of doing so. If unchecked, ketone concentrations increase progressively and lead to the development of a progressively serious metabolic acidosis. If unchecked, ketoacids accumulate and exceed the body's compensatory mechanisms (buffering with bicarbonate and hyperventilation) and H$^+$ concentration rises to the point where blood pH drops to around 6.7–6.8 (when total acids reach about 25 mmol litre^{-1}). Beyond this, the condition is rapidly fatal. Of considerable diagnostic importance is the fact that the ratio of the concentrations of 3-hydroxybutyric acid:acetoacetic acid is determined by the H$^+$ concentration such that the acetoacetic acid concentration decreases as blood pH decreases. Since the conventional bedside tests for ketones (Ketostix or Acetest tablets) react only with acetoacetic acid and require >1–2 mmol litre^{-1} acetoacetic acid to trigger a positive test, it is possible to have a patient with severe ketoacidosis with a plasma 3-hydroxybutyrate concentration as high as 20 mmol litre^{-1} and a urine ketone test showing only a trace of ketones (from a blood aceto-acetate concentration of 2 mmol litre^{-1}). This may often be ignored as irrelevant and the patient incorrectly assumed to have lactic acidosis; this can be a fatal mistake as the treatment of lactic acidosis is quite different from that of ketoacidosis.

Thus, there are two parallel metabolic processes that go wrong in the face of insulin deficiency: (i) glucose over-production and (ii) ketone over-production. Usually, both go wrong together and this is what one sees when insulin is withdrawn from a longstanding type 1 diabetic patient. Hyperglycaemia and ketoacidosis develop simultaneously and in parallel. Occasionally one pathway dominates. The commonest clinical scenario is hyperosmolar non-ketotic diabetic coma (HONK). This happens when insulin supplies are not quite zero and there is sufficient present to inhibit lipolysis but not gluconeogenesis. There is often an aggravating factor present: the patient may turn to a 'high-energy' drink to quench the thirst arising from the osmotic diuresis of the underlying type 2 diabetes. In the early stages, the patients may feel unwell and lacking in energy and, as a result of television advertising, try high-glucose drinks in the hope that they will make them feel more energetic. This just augments the already elevated rate of glucose entry into the circulation, aggravates osmotic diuresis and accelerates the process of decompensation. The very high glucose concentrations may themselves also help suppress lipolysis and ketogenesis by encouraging re-esterification of NEFA released from fat.

A rarer occurrence is 'normoglycaemic ketotacidosis'. This arises usually in an established diabetic patient who becomes unwell and cuts down food intake, monitors his/her own blood glucose and takes extra insulin to prevent hyperglycaemia. Occasionally the drive of fat-mobilizing hormones, such as catecholamines and growth hormone, break through the inhibition of insulin on lipolysis and ketosis results. However, this is very uncommon.

The development of electrolyte disturbances

During the hyperglycaemic phase when the hyperglycaemia-induced osmotic diuresis leads to thirst and polyuria, the choice of fluid that people make to slake their thirst varies enormously and often has a profound effect on outcome. We have already covered the scenario where a patient turns to a sweet beverage; in the case of another person who chooses a hypo-osmolar fluid such as water, the outcome may be quite different. In this case the fluid lost through the osmotic diuresis is nearly matched with the water intake and a tenuous 'compensated osmotic diuresis' exists and can be maintained for a long time. Despite this, electrolytes, particularly sodium, are continually lost with the diuresis. In the early stages of diuresis, sodium is lost at around 150 mmol litre^{-1} of urine (and potassium at around 5 mmol litre^{-1} of urine). If this is replaced by water, reasonable osmolar balance is maintained. The net result, however, is progressive depletion of sodium. This activates the renin–angiotensin system and aldosterone secretion increases, leading to increased sodium resorption from the tubules. Sodium losses decline as aldosterone concentrations increase. Aldosterone is very effective in retaining sodium even in the face of an osmotic diuresis. This hypersecretion of aldosterone has a knock-on effect on potassium stores since the high aldosterone concentrations reduce potassium resorption and urinary potassium excretion increases. The longer the phase of 'compensated' osmotic diuresis, where osmolar balance is maintained within reasonable limits, the greater the degree of overall sodium and potassium depletion. There is always also a 'free water deficit' as water, in the relative absence of sodium, is carried out with the diuresis.

Eventually, if untreated and if significant ketoacidosis does not develop, the sodium depletion reaches the stage where dehydration is so great that hypotension occurs. The patient then becomes oliguric and uraemic in the face of a substantial osmolar load. This is a very precarious situation characterized by a prune-like appearance with marked hypotension and raised serum creatinine and urea. If not treated promptly with parenteral rehydration, it is rapidly fatal. At this stage, the patient is depleted of, at the very least, 6 litres of water, 600 mmol of sodium and 500 mmol of potassium. Although the patient is so depleted of potassium, plasma potassium may be dangerously high as a result of potassium leaking out of cells into the extracellular fluid but no longer being excreted by diuresis. The most severe cases of fluid and electrolyte depletion are often seen in those who do not develop ketoacidosis. The depressed mental state correlates most closely with the degree of hyperosmolality and dehydration. Therapy should be targeted at correcting the electrolyte disturbance; insulin administration is of secondary importance.

If ketoacidosis does develop, the problems of metabolic acidosis may appear to dominate the clinical picture. It is important to remember, however, that severe fluid and electrolyte depletion is inevitable and that correction of this in a timely and appropriate manner is the hallmark of successful treatment.

Insulin replacement and the control of metabolism in diabetes

Current dogma would have us believe that administration of insulin to somebody with severely deranged diabetes suddenly and miraculously allows the cells in the body to breathe again and be restored to their former healthy state. This is, as we have seen, untrue, so it is amazing how long this dogma has persisted. A major aim of this review has been to set the record straight and rehabilitate Sir Edward Schafer's correct perception of the role of insulin in regulating energy metabolism. As has been outlined in the previous section, the major problems of lack of insulin are consequences of: (i) the osmotic diuresis resulting from the over-production of glucose or (ii) the metabolic acidosis resulting from the over-production of ketoacids. These occur as a result of a failure of insulin to regulate energy substrate release from stores in an orderly manner (chalonic action of insulin). The consequent metabolic mayhem results from the unrestrained release of all energy stores and flooding of the extracellular fluid with too much of what is normally a 'good thing'.

How then does insulin lower the blood glucose in diabetes?

Again this question is simple to answer and, by now, the answer will not be surprising. The use of tracer glucose infusions has shown not only that hyperglycaemia in the face of insulin deficiency is the result of over-production of glucose by the liver but also that insulin infusion lowers blood glucose by inhibiting hepatic glucose production. Indeed, rather than stimulating glucose uptake in tissues such as muscle, insulin in fact *reduces* glucose uptake. This is because the main factor driving glucose uptake is the 'mass action' effect of hyperglycaemia and the concentration gradient between the extracellular and intracellular glucose concentrations. Glucose transporters are *not* rate limiting under these conditions, even in the face of severe insulin deficiency.

Some of the experimental data behind our understanding of these mechanisms are illustrated in the results[2] shown in Fig. 6. In these studies a group of established type 1 diabetic patients volunteered to be studied on three occasions in the 'insulin-withdrawn' state 24 h after their last dose of insulin. The order of events was randomized. Patients received either an infusion of saline, low-dose insulin (2.6 u h^{-1}) or high-dose insulin (10.6 u h^{-1}) for 2 h. Tracer glucose was infused for 2 h before the insulin was started and the rates of glucose production and utilization were measured before and during the insulin infusions. Blood glucose concentration decreased more rapidly with high-dose rather than low-dose insulin and declined very slowly during the saline infusion (Fig. 6A). Insulin produced an immediate reduction of 50% in hepatic glucose production (R_a); this was the only change leading to the decrease in glucose during the low-dose study. The reduction in blood glucose concentration produced by the low-dose insulin infusion was followed by a reduction in glucose uptake (R_d) in keeping with the primary importance of the glucose concentration gradient rather than the insulin concentration in the regulation of glucose disposal. Thus insulin administration lowered glucose uptake into peripheral tissues. During the high-dose infusion there was a similar immediate halving of hepatic glucose production but insulin stimulated glucose uptake as well as inhibiting glucose production, so the decrease in blood glucose was more rapid (Fig. 6B). Under physiological conditions, plasma insulin concentrations rarely increase above 100 mu $litre^{-1}$ except transiently for

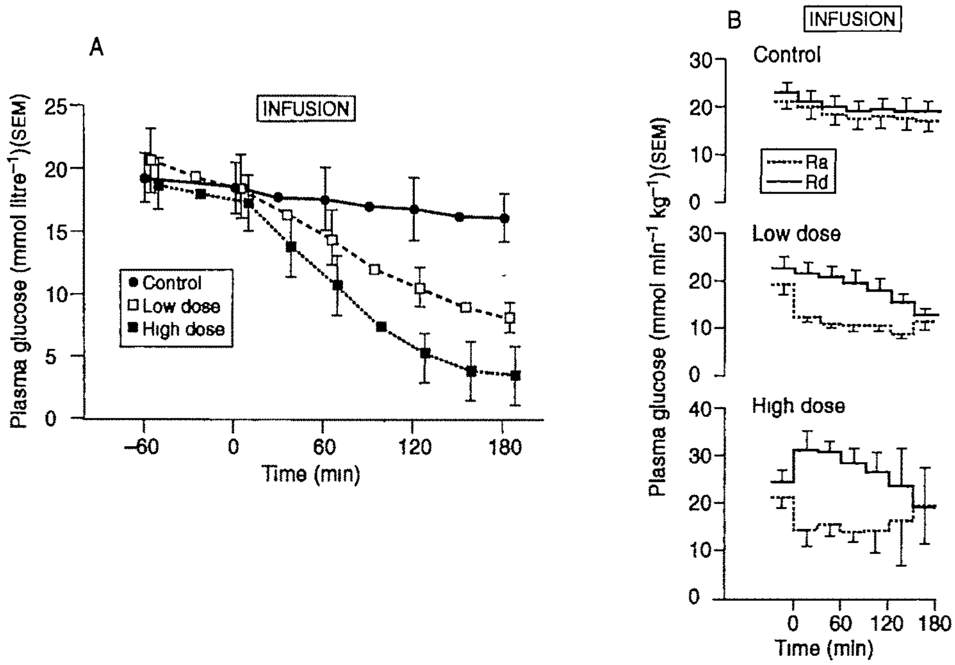

Fig 6 The data shown were obtained from a group of insulin-deprived patients with type 1 diabetes Each volunteer was studied on three occasions 24 h after his or her last dose of insulin (A) On each occasion the volunteers had a comparably increased fasting blood glucose concentration (as in Fig. 3). Each volunteer received an infusion of saline, low-dose insulin and high-dose insulin in random order (B) Glucose production and utilization were measured using a continuous infusion of tracer glucose. Corrections were made for measured urinary glucose losses The results show that fasting hyperglycaemia was caused by an elevated hepatic glucose production rate and that insulin lowered blood glucose through inhibition of hepatic glucose production. In the low-dose study (which produced insulin concentrations in the normal physiological range) glucose utilization was not increased at all; indeed, it fell in parallel with blood glucose concentration. In the high-dose study (which produced insulin concentrations of a magnitude seen only after a high-carbohydrate meal), there was a transient increase in glucose utilization but this was later followed by a progressive decrease in glucose.

a few minutes after a very high carbohydrate load. The low-dose infusion at 2.6 u h^{-1} produce insulin concentrations around 30–50 mU litre^{-1} whereas with 10.6 u h^{-1} concentrations may exceed 200 mU litre^{-1}, which is rarely seen in normal life. The results are very much in keeping with Schafer's concept of a primary role of insulin in regulating blood glucose concentration through control of hepatic glucose storage, hence the evolution of the endocrine pancreas within the portal circulation.

Why is it important to understand the mechanisms regulating energy metabolism?

Anaesthetists are involved in the management of many types of disease, both in the perioperative setting and in intensive care. Diabetes is a common condition and people with diabetes consume proportionally more health care resources than expected purely on the basis of prevalence. Modern management of diabetes in everyday life has been shown to affect outcome profoundly; the same is true in the perioperative and intensive care setting. The excellent review in this issue on the 'Anaesthetic management of patients with diabetes mellitus', by Professor Hall,[4] describes these advances in detail. The purpose of this article is to provide the modern science behind the practice of medicine. A clear understanding of the physiology and pathophysiology is essential if a doctor is going to react appropriately when they are faced with a clinical scenario in which they have to make decisions based on their understanding of disease rather than their personal experience of handling similar cases. Since this happens frequently in medicine, it is one of our obligations to keep up to date in our education. It is clear from the author's experience that there is a gap between modern science and teaching in this area.

We conclude this article by examining how this basic science approach might influence the management of a common clinical scenario; the well controlled, uncomplicated diabetic scheduled for elective surgery.

The well controlled diabetic undergoing elective surgery

The importance of good metabolic control

Tight metabolic control is important at all times for both type 1 and type 2 patients; it is especially so at the time of surgery. If control has been tight for the weeks preceding surgery, then at admission these patients are essentially normal with respect to fluid balance and electrolyte status.

Therefore, in respect to these issues, they can be treated in a similar way to other patients. This should greatly simplify the immediate preoperative preparation. Probably the most useful marker of the quality of recent control is the percentage of glycosylated haemoglobin, expressed as HbA1c (normal < 6.2%).

HbA1c is only a measure of recent *glycaemic* control; fortunately, however, in the vast majority of people with diabetes, if glycaemic control is good then so are other metabolic processes. Indeed, in patients with diabetes treated with insulin who have 'tight glycaemic control', there can be 'over-control' of other metabolic processes. This is explained as follows. Exogenous insulin is given peripherally and the dose adjusted to control hepatic glucose production, not proteolysis. With subcutaneous or intravenous administration of insulin, the concentration in the portal circulation will always be less than in the systemic circulation. This is a reversal of the normal situation. Good glycaemic control thus invariably results in peripheral hyperinsulinaemia. Hence lipolysis and proteolysis are slightly 'over-controlled' (protein synthesis is normal —insulin-independent and regulated by growth hormone— but protein breakdown is reduced as a result of the 'chalonic' action of peripheral hyperinsulinaemia).

A patient with an HbA1c of 7% is effectively normal. It is only when HbA1c is >9% that things begin to go wrong, especially with respect to the development of osmotic diuresis and consequent water and electrolyte loss. With an HbA1c of 12–15%, the patient is on the verge of diabetic ketoacidosis. In these patients, electrolyte imbalance, fluid balance and improvement in metabolic control must be corrected preoperatively.

Immediate preoperative metabolic control

Type 1 patients. Within a few years of the onset of diabetes, and even in the presence of excellent control, all type 1 diabetics stop producing endogenous insulin. Therefore, no type 1 diabetic can tolerate prolonged periods without exogenous insulin. Once the effect of their last dose of insulin has worn off, the brake on hepatic glucose production and catabolism is removed, resulting in the development over many hours of hyperglycaemia and ketosis. Traditionally, many of these patients have been managed with a mixture of glucose, insulin and potassium combined in one bag and administered intravenously. The use of separate infusions of glucose and insulin is also popular and probably allows tighter control, but has generated concern regarding the sudden discontinuation of the glucose if the bag finishes, a disconnection occurs or the cannula becomes obstructed (and is later flushed). Some of these concerns are equally valid if a saline infusion is used. However, as long as a well controlled type 1 patient continues their normal regimen (diet and insulin) up to the night before surgery (possibly modifying (reducing) their evening dose of insulin), then on the morning of operation their insulin concentrations will be low and decreasing and their glucose normal or slightly increased. In all other respects they remain well controlled. From then on the consequence of continued starvation combined with avoidance of insulin has to be the gradual development of hyperglycaemia as the liver starts releasing increasing amounts of glucose. It thus seems logical that the only intervention these patients require to maintain good control in the preoperative period is insulin. They should not yet have developed any fluid or electrolyte imbalance greater than that in a non-diabetic. Therefore, they could be managed more simply, more safely and with tight control by the sole use of an insulin infusion in combination with a traditional sliding scale. This greatly simplifies the physical administration of treatment (only one cannula, no three-way taps or 'Y' connectors with anti-reflux valves, no fluid pumps) and also avoids the complicated picture of matching insulin requirements to two variables: endogenous production of glucose and exogenous administration of glucose. The requirement for calories or fluid, or both, intra-operatively or later may require the commencement of a glucose, or other intravenous fluid, infusion at that time.

Type 2 patients. All type 2 diabetics, even those who require insulin for good control, produce endogenous insulin, and their metabolic state improves with fasting. Indeed studies have shown that prolonged starvation for up to 3 weeks normalizes glucose metabolism in type 2 patients. The immediate preoperative management of well controlled type 2 patients can and should be relatively simple. Normal treatment and diet should be continued up to the commencement of their preoperative fast (except, possibly, for reducing or omitting their evening dose of insulin or oral hypoglycaemic, respectively). Following their overnight fast they can safely omit the morning dose of insulin or oral hypoglycaemic and, apart from regular monitoring, no further intervention is likely to be necessary.

Intra- and post-operative management

The further management of all diabetic patients should be dictated by frequent assessment of glycaemic control and the patient's ability to resume a normal diet (see reference 4). Hyperglycaemia in any diabetic patient unable to take a normal diet should probably be treated with an intravenous infusion of insulin from an infusion pump, the rate being guided by a sliding scale. The need for intravenous calories and fluids should be assessed, as it would be for non-diabetics in a similar setting.

References

1 Brown BR Jr. Anaesthesia and endocrine disease. In: Prys-Roberts C, Brown BR Jr, eds. *International Practice of Anaesthesia* Oxford: Butterworth–Heinemann, 1996; 1/82/1–11

2 Brown P, Tompkins C, Juul S, Sonksen PH. Mechanism of action

of insulin in diabetic patients: a dose-related effect on glucose production and utilisation. *BMJ* 1978; **i**: 1239–42

3 Hall SE, Saunders J, Sonksen, PH. Glucose and free fatty acid turnover in normal subjects and in diabetic patients before and after insulin treatment. *Diabetologia* 1979; **16**: 297–306

4 McAnulty GR, Robertshaw HJ, Hall GM. Anaesthetic management of patients with diabetes mellitus. *Br J Anaesth* 2000; **85**: 80–90

5 Schafer E. *The Endocrine Organs*. London: Longman, Green & Co., 1916

6 Thomas SH, Wisher M, Brandenburg D, Sonksen PH. Insulin action on adipocytes: evidence that the anti-lipolytic and lipogenic effects of insulin are mediated by the same receptor. *Biochem J* 1979, **184**: 355–60

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Anaesthetic management of patients with diabetes mellitus

G. R. McAnulty[1], H. J. Robertshaw[2] and G. M. Hall[1*]

[1]Department of Anaesthesia and Intensive Care Medicine, St George's Hospital Medical School, London SW17 0RE, UK. [2]Department of Anaesthesia, Imperial College of Science, Technology and Medicine, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

**Corresponding author*

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The prevalence of diabetes mellitus in both adults and children has been steadily rising throughout the world for the past 20–30 yr.[29 55 97] Recent changes in diagnostic criteria, if widely adopted, will probably also lead to more patients being classified as having diabetes.[16] Inevitably, diabetic patients presenting for incidental surgery, or surgery related to their disease, will place an increasing burden on anaesthetic services. Conflict will occur between an economic need to minimize hospital stay and traditional approaches to managing perioperative diabetic patients that rely on a period of inpatient preoperative 'stabilization'.

Better glycaemic control in diabetic patients undergoing major surgery has been shown to improve perioperative mortality and morbidity.[44 90] Simple avoidance of hypoglycaemia and gross hyperglycaemia are no longer adequate in the light of this knowledge. While there can be little argument about the management of diabetic patients undergoing major procedures, their management for minor surgery is an increasing dilemma. Under what circumstances are day-case anaesthesia and surgery appropriate? Does admission on the day of surgery add to the risk for the diabetic patient? What investigations, if any, are needed to assess the cardiovascular system of an asymptomatic diabetic who presents for major surgery? Unfortunately, there are few data to provide answers to these questions. An understanding of the pathophysiology of diabetes and of the importance of recent research should improve the perioperative care of diabetic surgical patients. This review will discuss some recent developments in the field. It will not provide 'recipes' or algorithms for management. These can be found in any of the standard texts.

Revised diagnostic criteria for diabetes mellitus

Recently, both the American Diabetes Association (ADA) and the World Health Organization (WHO) published recommendations for new diagnostic criteria for diabetes mellitus.[1 106] Both bodies advise a reduction in the threshold limit for fasting plasma glucose concentrations and reaffirm a more aetiologically based nomenclature. The terms type 1 (pancreatic B-cell destruction) and type 2 (defective insulin secretion and, usually, insulin resistance) diabetes are recommended to replace completely the frequently misleading terms 'insulin-dependent' and 'non-insulin-dependent' diabetes. The ADA has specified that the diagnosis of diabetes mellitus should be made if a 'casual' (random) plasma glucose value in an asymptomatic individual is >11.1 mmol litre^{-1}. If a fasting plasma glucose is >7.0 mmol litre^{-1} (6.1 mmol litre^{-1} blood glucose) in an asymptomatic individual, the test should be repeated on a different day and a diagnosis made if the value remains above this limit. The ADA defines fasting plasma glucose concentrations between 6.1 and 7.0 mmol litre^{-1} (5.6–6.1 mmol litre^{-1} blood glucose) as representing 'impaired fasting glycaemia'. The WHO also recommends that a diagnosis of diabetes mellitus be made if a random plasma glucose concentration is >11.1 mmol litre^{-1} (venous whole blood >10.0 mmol litre^{-1}). It can also be diagnosed with a fasting plasma glucose concentration of >7.0 mmol litre^{-1} and a second similar test or an oral glucose tolerance test producing a result in the diabetic range.

The change in the fasting plasma glucose concentrations used to define diabetes and the role of a standard oral glucose tolerance test may make it difficult to compare epidemiological studies using these new criteria with those using previous ones. Inevitably, some individuals will be diagnosed as having diabetes using criteria based solely on (lower) fasting plasma glucose concentrations who would not have been so diagnosed under the earlier definitions. There will be others who would have fulfilled the definition using an oral glucose tolerance test but who will have acceptable fasting values. Thus it is likely that the new definitions will

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define as diabetic a group of glucose intolerant individuals.[52]

In addition to the two common types of diabetes, a number of causes of glucose intolerance can be defined according to a specific causal or pathological process. Gestational diabetes is glucose intolerance which has its onset in, or is first diagnosed during, pregnancy. The severity varies and the definition applies whether or not insulin is administered in treatment. Women with diabetes diagnosed before pregnancy are defined as having 'diabetes mellitus and pregnancy', not gestational diabetes.[1] The neonatal outcome of type 1 diabetic women who become pregnant is poor. Their infants are approximately five times more likely to be stillborn and 10 times more likely to have congenital malformations than those born to non-diabetic mothers.[10] Management in a specialist centre may improve the incidence of perinatal mortality.[34] Abnormally increased membrane transport of glucose, even in mothers whose diabetes is well controlled, may explain the continuing high rates of congenital malformations (particularly macrosomia) despite improved treatment.[48] Increasing the frequency of insulin administration from two to four times daily during pregnancy can lead to better maternal glycaemic control with a lower incidence of neonatal hypoglycaemia and hyperbilirubinaemia without increasing the risk of maternal hypoglycaemia.[73]

There is a number of rare genetic causes of glucose intolerance. Among these are defects of B-cell function (formerly called maturity-onset diabetes of the young, or MODY) and defects in insulin action (formerly called type A insulin resistance). Diffuse diseases of the exocrine pancreas (such as pancreatitis), specific viral infections which destroy pancreatic B cells (rubella, Coxsackie B, cytomegalovirus, mumps and others) and immune-mediated processes (insulin autoantibodies or insulin receptor antibodies) can also lead to a 'diabetic state'.[1] Endocrinopathies associated with excess secretion of counter-regulatory hormones (such as growth hormone, cortisol, glucagon and epinephrine) can lead to hyperglycaemia.

A number of drugs can induce glucose intolerance either by inhibiting the secretion of insulin or by interfering with the peripheral action of insulin.[1] In anaesthesia, glucocorticoids and adrenergic agonists are most frequently implicated. The new oral corticosteroid, deflazacort, may be less 'diabetogenic' than prednisolone or betamethasone.[2]

'Metabolic syndrome' (also called syndrome X or insulin resistance syndrome) is a non-causally linked cluster of symptoms which carry a high risk of macrovascular disease. The cluster includes impaired glucose tolerance or diabetes, insulin resistance, raised arterial pressure, raised plasma triglycerides, central obesity and microalbuminuria.[1]

Pathophysiology

Type 1 diabetics completely lack insulin secretion, making them prone to lipolysis, proteolysis and ketogenesis. These processes are inhibited by minimal levels of insulin secretion and are rare in type 2 diabetics unless there is an additional stress such as sepsis or dehydration.[122] Obviously, both groups are subject to the effects of hyperglycaemia.

Diabetics are at increased risk of myocardial ischaemia, cerebrovascular infarction and renal ischaemia because of their increased incidence of coronary artery disease,[94] arterial atheroma[51] and renal parenchymal disease.[14] Increased mortality is found in all diabetics undergoing surgery[44 90] and type 1 diabetics are particularly at risk of post-operative complications.[111] Increased wound complications are associated with diabetes[24 64 72 126] and anastomotic healing is severely impaired when glycaemic control is poor.[118]

The 'stress response' to surgery is associated with hyperglycaemia in non-diabetic patients as a result of increased secretion of catabolic hormones in the presence of a relative insulin deficiency. This deficiency arises from a combination of reduced insulin secretion[41] and insulin resistance.[109] Insulin resistance may result, in part, from the increase in secretion of catecholamines, cortisol and growth hormone[42] and involves an alteration of post-receptor binding of insulin and subsequent reduction of transmembrane glucose transport.[79] Some, at least, of the metabolic effects of the suppression of insulin secretion are reversed by intraoperative insulin infusion[37] and both oral and i.v. perioperative administration of glucose enhance postoperative glucose utilization rates.[56 62 80]

Adverse effects of hyperglycaemia

The consequences of a reduction in, or complete lack of, insulin-mediated metabolic processes can be classified according to chronicity and to histopathological effects.

Acute consequences of untreated, or inadequately treated, diabetes mellitus include dehydration (resulting from the osmotic diuretic effect of glycosuria), acidaemia (because of accumulation of lactic and/or ketoacids), fatigue, weight loss and muscle wasting (because of lipolysis and proteolysis in absolute insulin deficiency). Ketoacidosis is rare in type 2 diabetics but is frequently a presenting symptom of type 1 disease. It is a medical emergency that still carries a considerable mortality rate of up to 15%.[4 49] The mortality of hyperosmolar non-ketotic hyperglycaemic coma in type 2 diabetics may be even greater,[63] probably reflecting a more elderly population with a higher incidence of co-existing disease.

Ketoacidosis is treated by rehydration and insulin infusion with frequent measurements of serum electrolytes and acid–base status. Sequential estimations of blood β-hydroxybutyrate concentrations and concomitant continuation of intensive insulin therapy may expedite treatment.[124] Non-ketotic hyperglycaemic coma is frequently precipitated by infection and is commonly associated with multi-organ system dysfunction. Blood glucose concentrations may be extremely high.[33]

Chronic effects of diabetes can be divided into microvascular (including proliferative retinopathy and diabetic nephropathy), neuropathic (autonomic and peripheral neuropathies) and macrovascular complications (atherosclerotic disease). The incidence of microvascular and neuropathic complications in types 1 and 2 diabetics is similar when adjusted for duration of disease and quality of glycaemic control. The cumulative lifetime incidence of proliferative retinopathy, proteinuria and distal neuropathy is roughly 50% for both type 1 and type 2 diabetics. This implies that the primary cause of these complications is hyperglycaemia itself, as the underlying metabolic pathology is different for type 1 and type 2 disease.[31] Macrovascular complications (as measured by rates of coronary artery, cerebrovascular and peripheral vascular disease) are also similar for type 1 and 2 diabetics (cardiovascular mortality is 30–54% for type 1 and 38–41% for type 2 diabetes).[31] In type 2 patients, at least, abnormally high concentrations of plasminogen activator inhibitor-1 (PAI-1) and, therefore, impaired fibrinolysis, have been implicated in the accelerated rates of development of atherosclerotic disease.[83]

Improved glycaemic control has a beneficial effect on microvascular and neuropathic complications in type 2 diabetes.[114] Although there is probably no adverse effect,[83] improvement in glycaemic control alone appears not to improve the incidence of macrovascular disease in these patients.[114] However, tight control of blood pressure (with an angiotensin-converting enzyme inhibitor or a β-blocker) in patients with type 2 diabetes and hypertension reduces the risk of diabetes-related death, including that secondary to macrovascular complications, as well as the risk of other diabetes-related complications and eye disease.[115 116]

Diabetic therapy

The problems of insulin replacement

Insulin is secreted into the bloodstream from pancreatic B cells via the portal system so that there is normally a portal–peripheral insulin concentration gradient which cannot be mimicked by subcutaneous or i.v. insulin administration. Additionally, even the most sophisticated artificial insulin delivery systems cannot hope to replicate the complex local interaction between the B cells and A, D and PP cells of the islets of Langerhans (which secrete glucagon, somatostatin and pancreatic polypeptide, respectively) and the effects of the extrapancreatic neurohormonal system. Insulin secretion in response to varying states of feeding or starvation changes by 20- to 50-fold and maintains a basal insulin secretion during the fasting state. Insulin administered subcutaneously, even if timed optimally, will inevitably have inadequate peak concentrations for expected postprandial periods, and its duration of action may be frequently too short to avoid periods of hypoinsulinaemia and subsequent risk of lipolysis and proteolysis in patients with no endogenous insulin secretion.

Insulin is synthesized in the pancreas as part of a longer-chain protein called proinsulin. This is cleaved by membrane-bound proteases producing the polypeptides insulin and C-peptide. These two polypeptides are secreted into the circulation in equimolar amounts. C-peptide is useful experimentally in determining native insulin production in type 2 diabetic subjects receiving insulin. It was once thought that C-peptide had no physiological role other than facilitating the folding of the proinsulin molecule. However, more recent studies point to a possible role for C-peptide in glucose transport in skeletal muscle, renal tubular function and in the prevention of autonomic neuropathy.[119]

Hypoglycaemic therapy

Type 1 diabetics require insulin. Type 2 diabetics may require insulin but, in many cases, maintain reasonable glycaemic control with an appropriate diet and often the use of oral hypoglycaemic drugs.

Therapeutic insulin may be extracted from beef (now rarely used) or pork pancreas, or synthesized using recombinant DNA technology from *Escherichia coli*.[6] The amino acid sequences of insulin differ somewhat between species; however, modifying porcine insulin can produce human-sequence insulin. It was hoped that the replacement of animal- by human-sequence insulins would reduce the induction of antibodies and therefore insulin resistance, but clinical trials have been disappointing.[66]

The three types of insulin preparation are classified according to their length of action. Soluble insulins have a rapid onset and short duration of action (depending upon the route of administration). When injected subcutaneously the duration of action is from 30 min up to 8 h with a peak at 2–4 h. Human-sequence soluble insulin has a slightly shorter onset time and duration of action. Insulin lispro, a recently introduced recombinant human insulin analogue, has an even shorter duration of action. Soluble insulin injected i.v. has a half-life of approximately 5 min.[6]

Longer-acting insulin preparations are made with suspensions of insulin with either protamine ('isophane insulin') or zinc ('crystalline insulin') salts or both together. They are often administered in combination with soluble insulin to obtain rapid onset together with a long duration of action.[6] They are not suitable for i.v. use. Long-acting insulins may act for up to 36 h for animal-[91] and 24 h for human-sequence preparations.[47]

There are four groups of oral hypoglycaemic agents: the sulphonylureas, the biguanides, the (recently developed) thiazolidinediones and modifiers of glucose absorption from the gut. In the main, sulphonylureas enhance the secretion of insulin in response to glucose and increase sensitivity to its peripheral actions. Biguanides (metformin is the only compound in this group available in the UK) promote glucose utilization and reduce hepatic glucose production. Thiazolidinediones, which are still under clinical evaluation (and currently under a cloud because of reported hepatotoxicity), enhance insulin action in the periphery and inhibit hepatic gluconeogenesis, perhaps via a specific receptor mechanism. The α-glucosidase inhibitor, acarbose, suppresses the breakdown of complex carbohydrates in the gut and therefore delays the rise in postprandial blood glucose concentrations.[100]

Intensive, effective glycaemic control of type 2 diabetes results in a reduction of microvascular, but probably not macrovascular, complications of the disease.[31 114] Where adequate control can be achieved (haemoglobin A_{1c} concentration 7–8%[31]) there is no clear advantage for any therapeutic agent; oral hypoglycaemics and insulin have similar effects.[76] Metformin may be a better choice in obese type 2 diabetics. It was associated with a lower incidence of mortality and diabetes-related morbidity when used as a first-line treatment compared with either sulphonylureas or insulin in the recently-reported UK Prospective Diabetes Study (UKPDS).[113] However, addition of metformin to patients receiving sulphonylureas in the UKPDS was associated with a worrying increase in mortality. Despite concerns about rare but potentially lethal lactic acidosis, which may be more likely in the elderly,[100] in association with renal failure[25] and hepatic failure and after surgery,[71] metformin is well tolerated and less likely to cause hypoglycaemia than sulphonylureas or insulin.[28 113]

Interest in the potassium channel-blocking effect of sulphonylureas and, hence, interference with myocardial ischaemic preconditioning, has increased recently.[5] Glimepiride may not block potassium channels,[58] but angioplasty patients receiving sulphonylureas have greater mortality and morbidity than those given insulin.[30] The general implications of this observation are not clear but, until data from well-conducted studies are available, it would seem prudent to convert patients taking sulphonylureas to insulin several days before cardiac or other major surgery or procedures where myocardial perfusion may be compromised.

Perioperative therapy

Type 2 diabetics not receiving insulin and undergoing minor surgery usually can be managed satisfactorily without insulin.[108] However, diabetic patients scheduled for major surgery, who are receiving hypoglycaemic medication or who have poor glycaemic control, should be established on insulin therapy preoperatively. Continuous i.v. infusion of insulin is a better option than intermittent s.c. bolus regimens[11] and, at least in perioperative cardiac surgical patients, may be associated with improved outcome.[27] Although intermittent i.v. bolus regimens are still used,[87] this approach is difficult to recommend.[38 45]

Adsorption of insulin on to the surface of syringes, i.v. fluid bags and i.v. giving sets is an unavoidable problem. In solutions with a concentration of insulin of >400 ng ml^{-1} (~10 U $litre^{-1}$) the effect is minimal.[8] However, significant amounts of insulin may be adsorbed on to giving sets, particularly if they have a relatively high surface area, thereby reducing initial rates of insulin delivery if a high-volume, low-insulin concentration regimen is used.[69] More consistent delivery can be achieved with more concentrated solutions of lower volume administered from a syringe.[92]

When normal oral nutrition is not possible, parenteral administration of carbohydrate is required to safeguard against inadvertent hypoglycaemia and excessive catabolism. Safety is always a concern when insulin infusions are administered. Glucose–insulin–potassium (GIK) systems, such as the Alberti regimen, are inherently safe because they provide insulin and glucose in the same solution.[107] With separate glucose and insulin infusions one may be stopped inadvertently with potentially disastrous consequences. However, separate infusions were preferred by nursing staff and resulted in marginally improved perioperative glycaemic control when compared with a GIK system in one randomized controlled trial of 58 surgical patients.[101] Fifty per cent glucose solutions containing 0.25 or 0.5 U insulin ml^{-1} can provide amounts of glucose and insulin equivalent to the more conventional systems using 10% glucose and avoid the administration of large volumes of free water.[68] However, the hypertonic 50% solution needs to be infused into a central vein.

The metabolic challenge of surgery for the diabetic patient

The immediate perioperative problems facing the diabetic patient are: (i) surgical induction of the stress response with catabolic hormone secretion; (ii) interruption of food intake, which may be prolonged following gastrointestinal procedures; (iii) altered consciousness, which masks the symptoms of hypoglycaemia and necessitates frequent blood glucose estimations; and (iv) circulatory disturbances associated with anaesthesia and surgery, which may alter the absorption of subcutaneous insulin.

Surgery evokes the 'stress response', that is, the secretion of catecholamines, cortisol, growth hormone and, in some cases, glucagon. These hormones oppose glucose homeostasis, as they have 'anti-insulin' and hyperglycaemic effects. Gluconeogenesis is stimulated and peripheral glucose uptake decreased. Although diabetics need increased insulin during the perioperative period, requirements for glucose and insulin in this period are unpredictable and close monitoring is essential, especially in the unconscious or sedated patient.

Diabetic patients established on longer-acting insulin are at risk of hypoglycaemia if regular food intake is interrupted, and of lipolysis and proteolysis if insulin therapy is delayed. Postoperative wound healing and infection may be influenced by the adequacy of perioperative glycaemic control.[72 118]

Options for the perioperative management of diabetes

The main concern for the anaesthetist in the perioperative management of diabetic patients has been the avoidance of harmful hypoglycaemia; mild hyperglycaemia has tended to be seen as acceptable. This has been attributed to the difficulties of measuring blood glucose when the reduced level of consciousness perioperatively masks signs and symptoms of hypoglycaemia. However, in the past decade the availability of more accurate and easy-to-use glucose monitors, with evidence that good glycaemic control improves short-term outcome, makes the practice of 'permissive hyperglycaemia' unacceptable.

One survey of anaesthetic practice in the Oxford region of the UK suggests that anaesthetists are likely to manage hyperglycaemia in perioperative diabetic patients more aggressively now than they did in 1985.[22] However, of the 172 respondents in this survey, 22% still preferred to maintain blood glucose at >10 mmol litre^{-1} in diabetic patients and 2% preferred a value of >13 mmol litre^{-1}. The vast majority of respondents maintained glycaemic control for type 1 diabetic patients undergoing major surgery with glucose and insulin infusions, either separately or combined. Nearly 90% of respondents did not consider it necessary, in type 2 diabetics undergoing minor surgery, for there to be any greater intervention than omitting the usual hypoglycaemic therapy and avoidance of glucose-containing i.v. solutions. Surprisingly, 17% of senior anaesthetists had the same approach to type 2 diabetics undergoing major surgery. Cost and inconvenience may influence decisions about the intensity of blood glucose management and, until recently, there has been little evidence to support strategies aimed at tightening glycaemic control.[35] Between the two extremes of a diet-controlled stable type 2 diabetic presenting for minor surgery and the 'brittle' type 1 patient undergoing major abdominal surgery, about whom there is little argument, there remains considerable disagreement about the ideal regimen for managing blood glucose.

Monitoring techniques

The advent of semi-automated devices has improved the accuracy of measurement of blood and capillary glucose concentrations in both the community and hospital.[7] For these machines to be effective they must be calibrated regularly and people using them must be trained.

Recent work has suggested that measurement of circulating β-hydroxybutyrate concentrations may be helpful in treating acutely unstable diabetes[70 124] and the development of a bedside device will enable the usefulness of sequential estimations of ketonaemia to be assessed.[70]

Glycosylated haemoglobin (HbAc_1) measurement has no value in the perioperative period but is a valuable guide to long-term glycaemic control.[31] If HbAc_1 values have been consistently >8% it is probable that microvascular complications of diabetes are present.

Anaesthetic technique and the diabetic patient

Anaesthetic techniques, particularly the use of spinal, epidural, splanchnic or other regional blockade, may modulate the secretion of the catabolic hormones and any residual insulin secretion. The perioperative increase in circulating glucose, epinephrine and cortisol concentrations found in non-diabetic patients exposed to surgical stress under general anaesthesia is blocked by epidural anaesthesia.[39 125] The perioperative infusion of phentolamine, a competitive α-adrenergic receptor blocking drug, decreases the glycaemic response to surgery by partially reversing the suppression of insulin secretion.[75] Interestingly, a small study of non-diabetic patients showed preservation of the insulin response to a bolus of glucose after the use of low, but not high, spinal anaesthesia.[40] This implies that basal islet cell secretion is maintained by β-adrenergic stimulation. Whether extensive spinal blockade is detrimental in type 2 diabetics is not known. Cataract surgery in type 2 patients using local analgesia, when compared with general anaesthesia, was associated with much less disruption of glucose metabolism: blood glucose, lactate, β-hydroxybutyrate, serum cortisol, insulin and plasma non-esterified fatty acid concentrations were measured perioperatively.[3]

Diabetic patients undergoing surgery with neural blockade will usually resume oral intake earlier than after general anaesthesia. It is now common practice in cataract surgery to allow normal oral intake and hypoglycaemic therapy throughout the perioperative period. In a series of 12 000 cataract extractions under local anaesthesia, in which patients were not starved, eight patients showed evidence of brain stem anaesthesia, and one developed cerebral spread of local anaesthetic solution. In only one patient was surgery postponed because of persistent nausea.[43] However, the possibility of having to convert a regional technique to general anaesthesia may militate against this practice in other forms of surgery. At present, there is no evidence that regional anaesthesia alone, or in combination with general anaesthesia, confers any benefit in the diabetic surgical patient, in terms of mortality and major complications.

Regional anaesthesia may carry greater risks in the diabetic patient with autonomic neuropathy. Profound hypotension may occur with deleterious consequences in a patient with co-existing coronary artery, cerebrovascular or renovascular disease. The risks of infection and vascular damage may be increased with the use of regional techniques in diabetic patients; epidural abscesses occur more commonly following spinal and epidural anaesthesia.[54 77] Conversely, a diabetic peripheral neuropathy presenting after epidural anaesthesia may be confused with an anaesthetic complication of regional blockade.[50]

Anaesthetic agents and diabetes

Induction agents may affect glucose homeostasis perioperatively. Etomidate blocks adrenal steroidogenesis and hence cortisol synthesis, by its action on 11β-hydroxylase and cholesterol cleavage enzymes, and consequently decreases the hyperglycaemic response to surgery by approximately 1 mmol $litre^{-1}$ in non-diabetic subjects.[26] The effects on diabetic patients have not been established.

Benzodiazepines decrease the secretion of ACTH, and so the production of cortisol, when used in high doses during surgery.[18] They reduce sympathetic stimulation but, paradoxically, stimulate growth hormone secretion and result in a decrease in the glycaemic response to surgery. These effects are minimal when midazolam is given in usual sedative doses, but may be relevant if the drug is given by continuous i.v. infusion to patients in intensive care.

High-dose opiate anaesthetic techniques produce not only haemodynamic, but also hormonal and metabolic stability. These techniques effectively block the entire sympathetic nervous system and the hypothalamic–pituitary axis, probably by a direct effect on the hypothalamus and higher centres.[36] Abolition of the catabolic hormonal response to surgery will, therefore, abolish the hyperglycaemia seen in normal patients and may be of benefit in the diabetic patient.[59]

Halothane, enflurane and isoflurane, *in vitro*, inhibit the insulin response to glucose in a reversible and dose-dependent manner.[19 32] The effect of propofol on insulin secretion is not known. Diabetic patients show a reduced ability to clear lipids from the circulation.[123] Although this is unlikely to be relevant during short anaesthetics when propofol is used for maintenance or as an induction agent only, it may have implications for patients receiving propofol for prolonged sedation in the intensive care unit.

Complications of diabetes

Microvascular, neuropathic and macrovascular complications of diabetes mellitus are of special concern for the anaesthetist. Of particular importance are coronary heart disease, diabetic nephropathy and autonomic neuropathy because these may have a direct effect on the development of perioperative complications. In addition, young patients with long-standing type 1 diabetes and poor glycaemic control were found to have significantly decreased lung volume, lung diffusing capacity and cardiac stroke index during exercise when compared with patients treated with intensive insulin therapy.[78]

Because of glycosylation of collagen in the cervical joints, part of a generalized phenomenon called 'stiff joint syndrome',[98] diabetic patients are more likely to present with difficult laryngoscopy and intubation. Stiffness of the fourth and fifth interphalangeal joints is a common feature and the resulting alteration in palm print may be a good predictor of difficult intubation.[74] However, in one retrospective review of the anaesthetic records of 725 patients who underwent renal and/or pancreatic transplantation (of whom 209 were diabetic), none were reported as having 'moderate to extreme difficulty' of laryngoscopy. A total of 4.8% of the diabetics presented 'minimal to moderate' difficulty for intubation compared with 1.0% of the non-diabetics. All were intubated successfully although one was intubated electively with the aid of a fibre-optic flexible laryngoscope.[120]

Coronary heart disease

Diabetic men are more than four times as likely, and women five times as likely, to have coronary heart disease (CHD) than non-diabetics.[15] The annual cardiac event rate for untreated patients is 2.5% and even treated patients have more aggressive coronary disease and experience worse outcomes at any stage of the disease.[96] Some patients may have significant CHD causing myocardial ischaemia and even suffer myocardial infarction without typical symptoms. This may result from autonomic neuropathy,[67] but such 'silent ischaemia' is unlikely to occur without the co-existence of multiple risk factors. However, even selective screening targeted at patients with specific multiple risk factors has been discouraged because there is no evidence to support intervention (in the form of angioplasty or surgery) for asymptomatic diabetic patients.[99] What is the anaesthetist to do when presented with an asymptomatic diabetic patient who has some or all of the other risk factors such as advanced age, smoking, hyperlipidaemia and hypertension? Perioperative management of such a patient may be altered if it is known that there is a likelihood of myocardial ischaemia even if intervention by coronary artery bypass grafting or angioplasty (although perhaps not coronary stenting) carries an unacceptable risk:benefit ratio.[81] Asymptomatic type 1 diabetics with severe nephropathy scheduled for renal transplantation have been shown to benefit from preoperative screening and appropriate coronary revascularization.[65] A similar strategy may well be appropriate for high-risk diabetics, particularly those with 'metabolic syndrome', about to undergo major, elective non-cardiac surgery.

Diabetic patients have a worse outcome after coronary artery bypass surgery[96] and tend to stay in hospital longer.[60] They are more likely to develop postoperative renal failure[13] and suffer delayed stroke.[46] Deep sternal wound infection rates are also higher than in the non-diabetic population,[126] but the incidence may be reduced by improving diabetic control with continuous insulin infusions.[27] Mortality following coronary artery bypass surgery in diabetics is generally reported as significantly greater than that in non-diabetics.[110]

Diabetic nephropathy

In most countries, the leading causes of end-stage renal failure are hypertension and diabetes mellitus. In the USA, 30–40% of patients with type 1 diabetes will develop diabetic nephropathy and end-stage renal failure.[93] There is now substantial evidence that angiotensin-converting enzyme (ACE) inhibitors have a renal protective effect in patients with type 1 diabetes.[61] This may also be the case in type 2 diabetes, but the evidence is less convincing. No agent has been shown to be renoprotective in the perioperative period and some of the traditional drugs used for this purpose may be harmful.[17 105] Ensuring adequate renal perfusion by expanding the extracellular space (salt loading) or, more specifically, the intravascular space with appropriate haemodynamic monitoring may reduce the risk of postoperative renal dysfunction. Hydration with 0.45% sodium chloride solution alone provides better protection against radiocontrast medium-induced renal failure in at-risk subjects than saline with the addition of furosemide or mannitol.[102]

Autonomic neuropathy

Diabetic patients frequently develop neuropathy, most commonly a distal symmetrical sensory or sensorimotor polyneuropathy with a variable degree of autonomic involvement.[12] Autonomic dysfunction, which is of particular importance to the anaesthetist, is detectable in up to 40% of type 1[21] and 17% of type 2 diabetic patients.[23] Only a small proportion of these patients are symptomatic, with signs and symptoms such as gastroparesis, postural hypotension, gustatory sweating, diabetic diarrhoea and bladder paresis.[121] Many pathogenic mechanisms have been suggested for diabetic autonomic neuropathy, including local ischaemia,[112] tissue accumulation of sorbitol,[20] altered function of neuronal Na^+/K^+-ATPase pump activity[103] and immunologically mediated damage.[21]

The cardiovascular effects of insulin are paradoxical in autonomic neuropathy patients. In normal subjects, i.v. or s.c. insulin administration activates the sympathetic nervous system, causing an increase in circulating norepinephrine, supine arterial pressure and peripheral vascular resistance.[85] At the supraphysiological concentrations often used in the treatment of diabetes, vasodilation occurs with decreased peripheral vascular resistance and increased flow.[85] These observations suggest that insulin has dual effects, namely a vasoconstrictor effect mediated by the sympathetic nervous system at low insulin concentrations, and a vasodilator effect, perhaps mediated by nitric oxide release at higher concentrations. In patients with autonomic neuropathy, insulin causes a decrease in supine arterial pressure and exacerbates postural hypotension.

Detection of autonomic neuropathy in patients without symptoms has relied on methods such as assessment of heart rate variability (HRV).[104] In diabetic autonomic neuropathy, there is loss of HRV. The severe impairment of HRV in patients with end-stage diabetic nephropathy probably results from autonomic neuropathy and partly from co-existing heart disease.[57] The loss of HRV may be a contributory risk factor for ventricular arrhythmias and sudden death in these patients.[57] The presence of autonomic dysfunction in diabetics undergoing coronary artery surgery is not, however, automatically associated with haemodynamic instability during induction and the cardiovascular responses in non-diabetic and diabetic patients were very similar.[53]

Diabetic gastroparesis is characterized by a delay in gastric emptying without any gastric outlet obstruction.[117] The increased amount of gastric contents enhances the risk of acid aspiration during the induction of anaesthesia.[82] These patients are often asymptomatic and unpredictable difficulties in tracheal intubation increase even further the risk of aspiration.[88] Studies have shown little effect of prokinetic agents, such as cisapride, in reducing the volume of gastric contents in diabetics.[89]

Postoperative respiratory arrest seems to be more common in diabetic patients. Acute, unexpected respiratory problems in the recovery room are more common in men, in those aged >60 years, and in obese or diabetic patients.[95]

Wound healing and infection

It has long been recognized that wound healing is impaired in diabetic patients.[9 44] This observation has been repeated in animal models where it has been shown that pre- and postoperative glycaemic control with insulin, not postoperative alone, can restore normal anastomotic healing.[118] Recent work suggests that better glycaemic control with insulin infusions may reduce the incidence of deep sternal wound infections in diabetic patients who have undergone cardiac surgery.[27] This observation is supported by a study demonstrating better preservation of neutrophil function with 'aggressive' glycaemic control using an insulin infusion, compared with intermittent therapy, in diabetic cardiac surgical patients.[86] Interestingly, high-dose insulin and glucose infusions, aimed at maintaining supranormal plasma insulin concentrations and euglycaemia in non-diabetic burns patients, significantly decreased donor-site healing time after skin grafting.[84]

Conclusion

It is well known that diabetic patients are at greater risk of perioperative mortality and morbidity after major surgery and have a higher incidence of co-existing disease. Over recent years evidence has accumulated that improving glycaemic control in both the short and long term improves outcome. Attention to detail in the day-to-day management of the disease itself and associated conditions, such as hypertension, reduces the devastating consequences of microvascular and macrovascular complications. In addition, a more aggressive approach to glycaemic control in the perioperative period results in better wound healing, lower morbidity and shorter hospital stays. Gone are the days when anaesthetists could tolerate 'permissive hyperglycaemia' with the idea that this approach was in the patient's best interest. Tight metabolic control in the perioperative period is imperative and is a goal which is attainable in most patients.

References

1 Alberti KGMM, Zimmet PZ for the WHO Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 1998; **15**: 539–53

2 Anon. Deflazacort—an alternative to prednisolone? *Drug Ther Bull* 1999; **37**: 57–8

3 Barker JP, Robinson PN, Vafidis GC, Burrin JM, Sapsed-Byrne S, Hall GM. Metabolic control of non-insulin-dependent diabetic patients undergoing cataract surgery: comparison of local and general anaesthesia. *Br J Anaesth* 1995; **74**: 500–5

4 Basu A, Close CE, Jenkins D, Krentz AJ, Nattrass M, Wright AD. Persisting mortality in diabetic ketoacidosis. *Diabet Med* 1993; **10**: 282–4

5 Bijlstra PJ, den Arend JA, Lutterman JA, Russel FG, Thien T, Smits P Blockade of ATP-sensitive potassium channels reduces the vasodilator response to ischaemia in humans. *Diabetologia* 1996; **39**: 1562–8

6 *British National Formulary*. London: British Medical Association, Royal Pharmaceutical Society of Great Britain, 1999: 302–6

7 Brunner GA, Ellmerer M, Sendlhofer G *et al* Validation of home blood glucose meters with respect to clinical and analytical approaches. *Diabetes Care* 1998; **21**: 585–90

8 Canivet B, Berre A, Macchi P, Grimaud D, Maestracci P, Freychet P. Adsorption de l'insuline introduite directement dans les flacons de perfusion. *Sem Hop Paris* 1983; **59**: 1405–8

9 Casey J, Flinn WR, Yao JS, Fahey V, Pawlowski J. Correlation of immune and nutritional status with wound complications in patients undergoing vascular operations. *Surgery* 1983; **93**: 822–7

10 Casson IF, Clarke CA, Howard CV *et al*. Outcomes of pregnancy in insulin dependent diabetic women. results of a five year population cohort study. *Br Med J* 1997; **315**: 275–8

11 Christiansen CL, Schurizek BA, Malling B, Knudsen L, Alberti KG, Hermansen K. Insulin treatment of the insulin-dependent diabetic patient undergoing minor surgery. Continuous intravenous infusion compared with subcutaneous administration. *Anaesthesia* 1988; **43**: 533–7

12 Comi G, Corbo M. Metabolic neuropathies. *Curr Opin Neurol* 1998; **11**: 523–9

13 Conolon PJ, Stafford-Smith M, White WD *et al*. Acute renal failure following cardiac surgery. *Nephrol Dialysis Transplant* 1999; **14**: 1158–62

14 Culleton BF, Larson MG, Evans JC *et al*. Prevalence and correlates of elevated serum creatinine levels· the Framingham Heart Study. *Arch Intern Med* 1999; **159** 1785–90

15 Curry CJ, Morgan CL, Peters JR. Patterns and costs of hospital care for coronary heart disease related and not related to diabetes. *Heart* 1997; **78**: 544–9

16 DECODE Study Group, on behalf of the European Diabetes Epidemiology Study Group Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data *Br Med J* 1998; **317**: 371–5

17 Denton MD, Chertow, GM, Brady HR. 'Renal-dose' dopamine for the treatment of acute renal failure· Scientific rationale, experimental studies and clinical trials. *Kidney Int* 1996, **49**: 4–14

18 Desborough JP, Hall GM, Hart GR, Burrin JP. Midazolam modifies pancreatic and anterior pituitary secretion during upper abdominal surgery. *Br J Anaesth* 1991; **67**: 390–96

19 Desborough JP, Jones PM, Persaud SJ, Landon MJ, Howell SL. Isoflurane inhibits insulin secretion in isolated rat pancreatic islets of Langerhans *Br J Anaesth* 1993, **71**: 873–6

20 Dyck P, Zimmerman B, Vilen T Nerve glucose, fructose, sorbitol and myoinositol, and fiber degeneration and regeneration in diabetic neuropathy *New Engl J Med* 1988, **319**· 542

21 Ejskaer NT, Zanone MM, Peakman M Autoimmunity in diabetic autonomic neuropathy: Does the immune system get on your nerves? *Diabet Med* 1998; **15**: 723–9

22 Eldridge AJ, Sear JW. Peri-operative management of diabetic patients: any changes for the better since 1985? *Anaesthesia* 1996; **51**: 45–51

23 Flynn MD, O'Brien IA, Corrall RJ. The prevalence of autonomic and peripheral neuropathy in insulin-treated diabetic subjects. *Diabet Med* 1995; **12**: 310–3

24 Folk JW, Starr AJ, Early JS. Early wound complications of operative treatment of calcaneus fractures: analysis of 190 fractures. *J Orthop Trauma* 1999; **13**: 369–72

25 de Fronzo RA, Goodman AM Multicentre Metformin Study Group: efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *New Engl J Med* 1995, **333**. 541–9

26 Fragen RJ, Shanks CA, Molteni A, Avram MJ. Effects of etomidate on hormonal responses to surgical stress. *Anesthesiology* 1984; **61**· 652–6

27 Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg* 1999, **67** 352–60

28 Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial *Am J Med* 1997, **103**: 491–7

29 Gardner SG, Bingley PJ, Sawtell PA, Weeks S, Gale EAM. Rising incidence of insulin dependent diabetes in children aged under 5 years in the Oxford region: time trend analysis. *Br Med J* 1997; **315**: 713–17

30 Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR Jr. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1999; **33**. 119–24

31 Gaster B, Hirsch IB. The effects of improved glycemic control on complications in type 2 diabetes. *Arch Intern Med* 1998; **158**. 134–40

32 Gingerich R, Wright PH, Paradise RR. Inhibition by halothane of glucose-stimulated insulin secretion in isolated pieces of rat pancreas. *Anesthesiology* 1974; **40**: 449–52

33 Gupta S, Prabhu MR, Gupta MS, Niblett D. Severe non-ketotic hyperosmolar coma—intensive care management. *Eur J Anaesthesiol* 1998 **15**: 603–6

34 Hadden DR. How to improve prognosis in type 1 diabetic pregnancy. Old problems, new concepts. *Diabetes Care* 1999; **22** (suppl. 2): B104–8

35 Hall GM, Desborough JP Diabetes and anaesthesia. slow progress? *Anaesthesia* 1988; **43**· 531–2

36 Hall GM, Lacoumenta S, Hart GR, Burrin JP. Site of action of

fentanyl in inhibiting the pituitary-adrenal response to surgery in man. *Br J Anaesth* 1990; **65**: 251–3

37 Hall GM, Walsh ES, Paterson JL, Mashiter K. Low-dose insulin infusion and substrate mobilisation during surgery. *Br J Anaesth* 1983; **55**: 939–45

38 Hall GM. Insulin administration in diabetic patients: return of the bolus? *Br J Anaesth* 1994: **72**: 1–2

39 Hall GM. The anaesthetic modification of the endocrine and metabolic response to surgery. *Ann R Coll Surg Engl* 1985; **67**: 25–9

40 Halter JB, Pflug AE. Effect of sympathetic blockade by spinal anesthesia on pancreatic islet cell function in man. *Am J Physiol* 1980; **239**: E150–5

41 Halter JB, Pflug AE. Effects of anesthesia and surgical stress on insulin secretion in man. *Metabolism* 1980; **29** (suppl. 1): 1124–7

42 Halter JB, Pflug AE. Relationship of impaired insulin secretion during surgical stress to anesthesia and catecholamine release. *J Clin Endocrinol Metab* 1980; **51**: 1093–8

43 Hamilton RC, Gimbel HV, Strunin L. Regional anaesthesia for 12,000 cataract extraction and intraocular lens implantation procedures. *Can J Anaesth* 1988; **35**: 615–23

44 Hickman MS, Schwesinger WH, Page CP. Acute cholecystitis in the diabetic. A case–control study of outcome. *Arch Surg* 1988; **123**: 409–11

45 Hirsch IB, McGill JB, Cryer PE, White PF. Perioperative management of surgical patients with diabetes mellitus. *Anesthesiology* 1991; **74**: 346–59

46 Hogue CW, Murphy SF, Schechtman KB, Davila-Roman VG. Risk factors for early or delayed stroke after cardiac surgery. *Circulation* 1999; **100**: 642–7

47 Holman RR, Steemson J, Darling P, Reeves WG, Turner RC. Human ultralente insulin. *Br Med J* 1984; **288**: 665–8

48 Jansson T, Wennergren M, Powell TL. Placental glucose transport and GLUT 1 expression in insulin-dependent diabetes. *Am J Obstet Gynaecol* 1999; **180**: 163–8

49 Japan and Pittsburgh Childhood Diabetes Research Groups. Coma at the onset of young insulin-dependent-diabetes in Japan: the results of a nationwide survey. *Diabetes* 1985; **34**: 1241–6

50 Kahn L. Neuropathies masquerading as an epidural complication. *Can J Anaesth* 1997; **44**: 313–16

51 Keen H, Jarrett RJ, Fuller JH, McCartney P. Hyperglycemia and arterial disease. *Diabetes* 1981; **30** (suppl. 2): 49–53

52 Keen H. Impact of new criteria for diabetes on pattern of disease. *Lancet* 1998; **352**: 1000–1

53 Keyl C, Lemberger P, Palitzsch KD, Hochmuth K, Liebold A, Hobbhahn J. Cardiovascular autonomic dysfunction and hemodynamic response to anesthetic induction in patients with coronary artery disease and diabetes mellitus. *Anesth Analg* 1999; **88**: 985–91

54 Kindler CH, Seeberger MD, Staender SE. Epidural abscess complicating epidural anesthesia and analgesia. An analysis of the literature. *Acta Anaesthesiol Scand* 1998; **42**: 614–20

55 King H, Rewers M. Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. *Diabetes Care* 1993; **16**: 157–77

56 Kingston WJ, Livingston JN, Moxley RT. Enhancement of insulin action after oral glucose ingestion. *J Clin Invest* 1986; **77**: 1153–62

57 Kirvela M, Salmela K, Toivonen L, Koivusalo A-M, Lindgren L. Heart rate variability in diabetic and non-diabetic renal transplant patients. *Acta Anaesthesiol Scand* 1996; **40**: 804–8

58 Klepzig H, Kober G, Matter C *et al.* Sulfonylureas and ischaemic preconditioning; a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. *Eur Heart J* 1999; **20**: 439–46

59 Klingstedt C, Giesecke K, Hamberger B, Jarnberg PO. High and low dose fentanyl anaesthesia: circulatory and plasma catecholamine responses during cholecystectomy. *Br J Anaesth* 1987; **59**: 184–8

60 Lazar HL, Fitzgerald C, Gross S, Heeren T, Aldea GS, Shemin RJ. Determinants of length of stay after coronary artery bypass graft surgery. *Circulation* 1995; **92** (suppl II): 20–4

61 Lewis EJ, Hunsicker LG, Bain RP, Rohde RD for the Collaborative Study Group: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *New Engl J Med* 1993; **329**: 1456–62

62 Ljungqvist O, Thorell A, Gutniak M, Haggmark T, Efendic S. Glucose infusion instead of preoperative fasting reduces postoperative insulin resistance. *J Am Coll Surg* 1994; **178**: 329–6

63 Lorber D. Nonketotic hypertonicity in diabetes mellitus. *Med Clin North Am* 1995; **79**: 39–52

64 Maher M, Singh HP, Dias S, Street J, Aherne T. Coronary artery bypass surgery in the diabetic patient. *Ir J Med Sci* 1995; **164**: 136–8

65 Manske CL, Wang Y, Rector T, Wilson RF, White CW. Coronary revascularisation in insulin-dependent diabetic patients with chronic renal failure. *Lancet* 1992; **340**: 998–1002

66 Maran A, Lomas J, Archibald H, Macdonald IA, Gale EA, Amiel SA. Double blind clinical and laboratory study of hypoglycaemia with human and porcine insulin in diabetic patients reporting hypoglycaemia unawareness after transferring to human insulin. *Br Med J* 1993; **306**: 167–71

67 Marchant B, Umachandran V, Stevenson R, Kopelman PG, Timmis AD. Silent myocardial ischaemia with and without diabetes. *J Am Coll Cardiol* 1993; **22**: 1433–7

68 McAnulty GR, Robertshaw HJ, Berge D, Barnardo P, Hall GM. Insulin concentrations from stored glucose–insulin–potassium ('GIK') solutions: an improved system. *Br J Anaesth* 1999; **82** (suppl. 1): 129

69 McAnulty GR, Robertshaw HJ, Hall GM. Insulin concentrations in samples from stored glucose–insulin–potassium ('GIK') bags. *Br J Anaesth* 1998; **80** (suppl. 1): 91–2

70 McBride MO, Smye M, Nesbit GS, Hadden DR. Bedside blood ketone monitoring. *Diabet Med* 1991; **8**: 688–90

71 Merckner SK, Maier C, Neumann G, Wulf H. Lactic acidosis as a serious complication of antidiabetic biguanide medication with metformin. *Anesthesiology* 1997; **87**: 1003–5

72 Mossad SB, Serkey JM, Longworth DL, Cosgrove DM, Gordon SM. Coagulase-negative staphylococcal sternal wound infections after open-heart operations. *Ann Thorac Surg* 1997; **63**. 395–401

73 Nachum Z, Ben-Shlomo I, Weiner E, Shalev E. Twice daily versus four times daily insulin regimens for diabetes in pregnancy: randomised controlled trial. *Br Med J* 1999; **319**: 1223–7

74 Nadal JLY, Fernandez BG, Escobar IC, Black M, Rosenblatt WH. The palm print as a sensitive predictor of difficult laryngoscopy in diabetics. *Acta Anaesthesiol Scand* 1998; **42**: 199–203

75 Nakao K, Miyata M. The influence of phentolamine, an adrenergic blocking agent, on insulin secretion during surgery. *Eur J Clin Invest* 1977; **7**: 41–5

76 Nathan DM. Some answers, more controversy, from UKPDS. *Lancet* 1998; **352**: 832–3

77 Nikolajsen L, Ilkjaer S, Christensen JH, Krøner K, Jensen TS. Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom limb pain in lower-limb amputation. *Lancet* 1997; **350**: 1353–7

78 Niranjan V, McBrayer DG, Ramirez LC, Raskin P, Hsia CCW. Glycemic control and cardiopulmonary function in patients with insulin-dependent diabetes mellitus. *Am J Med* 1997; **103**: 504–13

79 Nordenstrom J, Sonnenfield T, Arner P. Characterization of insulin resistance after surgery. *Surgery* 1989; **105**: 28–35

80 Nygren J, Soop M, Thorell A, Efendic S, Nair KS, Ljungqvist O.

Preoperative oral carbohydrate administration reduces postoperative insulin resistance. *Clin Nutr* 1998; **17**: 65–71

81 O'Neill WW. Multivessel balloon angioplasty should be abandoned in diabetic patients! *J Am Coll Cardiol* 1998; **31**: 20–2

82 Olsson GL, Hallen B, Hambraeus-Jonzon K. Aspiration during anaesthesia: a computer-aided study of 185,358 anaesthetics. *Acta Anaesthesiol Scand* 1986; **30**: 84–92

83 Panahloo A, Yudkin JS. Diminished fibrinolysis in diabetes mellitus and its implication for diabetic vascular disease. *J Cardiovasc Risk* 1997; **4**: 91–9

84 Pierre EJ, Barrow RE, Hawkins HK *et al.* Effects of insulin on wound healing. *J Trauma* 1998; **44**: 342–5

85 Porcellati F, Fanelli C, Bottini P *et al.* Mechanisms of arterial hypotension after therapeutic dose of subcutaneous insulin in diabetic autonomic neuropathy. *Diabetes* 1993, **42**: 1055–64

86 Rassias AJ, Marrin CA, Arruda J, Whalen PK, Beach M, Yeager MP Insulin infusion improves neutrophil function in diabetic cardiac surgery patients. *Anesth Analg* 1999; **88**. 1011–6

87 Raucoules-Aime M, Labib Y, Levraut J, Gastaud P, Dolisi C, Grimaud D. Use of i.v. insulin in well-controlled non-insulin-dependent diabetics undergoing major surgery. *Br J Anaesth* 1996; **76**: 198–202

88 Reissell E, Orko R, Maunuksela E.-L, Lindgren L. Predictability of difficult laryngoscopy in patients with long-term diabetes mellitus *Anaesthesia* 1990; **45**: 1024–7

89 Reissell E, Taskinen M.-R, Orko R, Lindgren L. Increased volume of gastric contents in diabetic patients undergoing renal transplantation: lack of effect with cisapride. *Acta Anaesthesiol Scand* 1992; **36**: 736–40

90 Risum O, Abdelnoor M, Svennevig JL *et al.* Diabetes mellitus and morbidity and mortality risks after coronary artery bypass surgery. *Scand J Thorac Cardiovasc Surg* 1996; **30**: 71–5

91 Rizza RA, O'Brien PC, Service FJ. Use of beef ultralente for basal insulin delivery. plasma insulin concentrations after chronic ultralente administration in patients with IDDM. *Diabetes Care* 1986; **9**: 120–23

92 Robertshaw HJ, McAnulty GR, Berge D, Barnardo P, Hall GM. Pre-prepared glucose-insulin-potassium ('GIK') syringes: a practical alternative alternative to 'GIK' bags. *Br J Anaesth* 1999; **82** (suppl. 1): 129

93 Rodby RA, Firth LA, Lewis EJ for the Collaborative Study Group. An economic analysis of captopril in the treatment of diabetic nephropathy. *Diabetes Care* 1996; **19**: 1051–61

94 Rodriguez BL, Lau N, Burchfiel CM *et al.* Glucose intolerance and 23-year risk of coronary heart disease and total mortality: the Honolulu Heart Program. *Diabetes Care* 1999; **22**: 1262–5

95 Rose DK, Cohen MM, Wigglesworth DF, DeBoer DP. Critical respiratory events in the postanesthesia care unit. *Anesthesiology* 1994; **81**: 410–8

96 Rutter MK, Marshall SM, McComb JM. Coronary artery disease and diabetes. *Heart* 1997; **78**: 527–8

97 Ruwaard D, Hirasing RA, Reeser HM *et al.* Increasing incidence of type I diabetes in The Netherlands. The second nationwide study among children under 20 years of age. *Diabetes Care* 1994; **17**: 599–601

98 Salzarulo HH, Taylor LA. Diabetic "stiff joint syndrome" as a cause of difficult intubation *Anesthesiology* 1986; **64**: 366–8

99 Sayer JW, Timmis AD Investigation of coronary artery disease in diabetes: is screening of asymptomatic patients necessary? *Heart* 1997; **78**: 525–6

100 Scheen AJ, Lefèbvre PJ. Oral antidiabetic agents: a guide to selection *Drugs* 1998; **55**: 225–36

101 Simmons D, Morton K, Laughton SJ, Scott DJ A comparison of two intravenous insulin regimens among surgical patients with insulin-dependent diabetes mellitus. *Diabetes Education* 1994, **20**: 422–7

102 Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *New Engl J Med* 1994; **331**: 1416–20

103 Stevens MJ. Nitric oxide as a potential bridge between the metabolic and vascular hypotheses of diabetic neuropathy *Diabet Med* 1995; **12**: 292–5

104 Stys A, Stys T. Current clinical applications of heart rate variability. *Clin Cardiol* 1998; **21**: 719–24

105 Tang AT, El-Gamel A, Keevil B, Yonan N, Deiraniya AK. The effect of 'renal-dose' dopamine on renal tubular function following cardiac surgery assessed by measuring retinol binding protein (RBP). *Eur J Cardiothorac Surg* 1999; **15**: 717–21

106 The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 1997; **20**: 1183–97

107 Thomas DJ, Platt HS, Alberti KG Insulin-dependent diabetes during the peri-operative period. An assessment of continuous glucose–insulin–potassium infusion, and traditional treatment. *Anaesthesia* 1984; **39**: 629–37

108 Thompson J, Husband DJ, Thai AC, Alberti KG. Metabolic changes in the non-insulin-dependent diabetic undergoing minor surgery: effect of glucose–insulin–potassium infusion. *Br J Surg* 1986; **73**: 301–4

109 Thorell A, Nygren J, Hirshman MF *et al.* Surgery-induced insulin resistance in human patients: relation to glucose transport and utilization. *Am J Physiol* 1999; **276**: E754–61

110 Thourani VH, Weintraub WS, Stein B, Gebhart SS, Craver JM, Jones EL, Guyton RA Influence of diabetes on early and late outcome after coronary artery bypass grafting. *Ann Thorac Surg* 1999; **67**: 1045–52

111 Treiman GS, Treiman RL, Foran RF *et al* The influence of diabetes mellitus on the risk of abdominal aortic surgery. *Am Surg* 1994; **60**: 436–40

112 Tuck RR, Schmelzer J, Low P. Endoneurial blood flow and oxygen tension in the sciatic nerves of rats with experimental diabetic neuropathy *Brain* 1984; **107**: 935–50

113 UK Prospective Diabetes Study (UKPDS) Group Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352**: 854–65

114 UK Prospective Diabetes Study (UKPDS) Group Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998, **352**: 837–53

115 UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *Br Med J* 1998; **317**: 713–20

116 UK Prospective Diabetes Study Group Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes UKPDS 38 *Br Med J* 1998; **317**: 703–12

117 Varis K. Diabetic gastroparesis. *Scand J Gastroenterol* 1989; **24**: 897–903

118 Verhofstad HJ, Hendriks T. Complete prevention of impaired anastomotic healing in diabetic rats requires preoperative blood glucose control *Br J Surg* 1996; **83**: 1717–21

119 Wahren J, Johansson B-L, Wallberg-Henriksson H. Does C-peptide have a physiological role? *Diabetologia* 1994; **37** (suppl. 2): S99–107

120 Warner ME, Contreras MG, Warner MA, Schroeder DR, Munn SR, Maxson PM Diabetes mellitus and difficult laryngoscopy in renal and pancreatic transplant patients. *Anesth Analg* 1998; **86**. 516–19

121 Watkins PJ. Clinical observations and experiments in diabetic neuropathy. *Diabetologia* 1992; **35**: 2–11

122 Westphal SA. The occurrence of diabetic ketoacidosis in non-insulin-dependent diabetics and newly diagnosed diabetic adults. *Am J Med* 1996; **101**: 19–24

123 Wicklmayr M, Rett K, Dietz G, Mehnert H. Comparison of metabolic clearance rates of MCT/LCT and LCT emulsions in diabetics. *J Parenteral Enteral Nutr* 1988; **12**: 68–71

124 Wiggam MI, O'Kane MJ, Harper R et *al.* Treatment of diabetic ketoacidosis using normalization of blood 3-hydroxybutyrate concentration as the endpoint of emergency management. *Diabetes Care* 1997; **20**: 1347–52

125 Wolf AR, Eyres RL, Laussen PC *et al.* Effect of extradural analgesia on stress responses to abdominal surgery in infants. *Br J Anaesth* 1993; **70**: 654–60

126 Zacharias AZ, Habib RH. Factors predisposing to median sternotomy complications. *Chest* 1996; **110**: 1173–8

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Obesity in anaesthesia and intensive care

J. P. Adams and P. G. Murphy

Department of Anaesthesia, The General Infirmary at Leeds, Great George Street, Leeds LS1 3EX, UK

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The prevalence of significant obesity continues to rise in both developed and developing countries, and is associated with an increased incidence of a wide spectrum of medical and surgical pathologies[35] (Table 1). As a result, the anaesthetist can expect to be presented frequently with obese patients in the operating theatre, intensive care unit or resuscitation room. These patients may provide the anaesthetist with a considerable challenge. A thorough understanding of the pathophysiology and specific complications associated with the condition should allow more effective and safer treatment for this unique group of patients.

Definitions

Obesity is a condition of excessive body fat. The name is derived from the Latin word *obesus*, which means fattened by eating.[69] The difference between normality and obesity is arbitrary, but an individual must be considered obese when the amount of fat tissue is increased to such an extent that physical and mental health are affected and life expectancy reduced.[122] Examples of body fat contents in adults from Western societies are 20–30% for the average female, 18–25% for the average male, 10–12% for a professional soccer player and 7% for a marathon runner.[121]

Accurate measurement of body fat content is difficult and requires sophisticated techniques such as computed tomography (CT) scanning or magnetic resonance imaging. Useful estimates, however, can be obtained by evaluating weight for a given height and then comparing that figure with an ideal weight. The concept of ideal body weight (IBW) originates from life insurance studies which describe the weight associated with the lowest mortality rate for a given height and gender; for general clinical purposes, IBW can be estimated from the formula IBW (in kg) = height (in cm) – x, where x is 100 for adult males and 105 for adult females.

The body mass index (BMI) is a more robust measure of the relationship between height and weight, and is widely used in clinical and epidemiological studies. It is calculated as follows:

$$\text{BMI} = \text{body weight (in kg)}/\text{height}^2\text{ (in metres)}$$

A BMI of <25 kg m^{-2} is considered normal; a person with a BMI of 25–30 kg m^{-2} is considered overweight but at low risk of serious medical complications, while those with a BMI of >30, >35 and >55 kg m^{-2} are considered obese, morbidly obese and super-morbidly obese, respectively.[39] Morbidity and mortality rise sharply when the BMI is >30 kg m^{-2}.[76] Although it is a very robust and practical assessment of obesity, the BMI does have its limitations. For instance, heavily muscled individuals would be classified as overweight It is now thought that other factors, such as young age and the pattern of adipose tissue distribution, may be better predictors of health risk.

Epidemiology

There is overwhelming evidence that the prevalence of obesity is increasing worldwide. In 1997, an International Obesity Task Force summarized information on the epidemiology of obesity.[35] Defining obesity as a BMI of >30 kg m^{-2}, they concluded that the prevalence of obesity was 15–20% in Europe with wide regional variations In the UK over the period 1980–1991 the prevalence of obesity had increased from 6% to 13% in men and from 8% to 15% in women, meaning that the average UK body weight had risen by approximately 1 kg over that 10 yr period. The picture was better for Scandinavia and the Netherlands (10%) but worse for Eastern Europe (up to 50% among women in some countries). The health and economic implications are considerable, since countries such as France, Germany and the UK will each have approximately 10 million obese inhabitants.[35] The situation in the USA is even worse, with the prevalence of a BMI of >25 kg m^{-2} being 59.4% for men, 50.7% for women and 54.9% for adults overall.[70] Furthermore, for the period 1960–1994, the prevalence of obesity (BMI of >30 kg m^{-2}) has increased markedly from 12.8% to 22.5%.

The prevalence of obesity varies with socioeconomic status. In developed countries, poverty is associated with a greater prevalence of obesity whereas in developing areas it is affluence that carries the higher risk.[147]

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Table 1 Medical and surgical conditions associated with obesity

Category	Examples
Cardiovascular disease	Sudden (cardiac) death; obesity cardiomyopathy, hypertension, ischaemic heart disease; hyperlipidaemia; cor pulmonale, cerebrovascular disease, peripheral vascular disease, varicose veins, deep-vein thrombosis and pulmonary embolism
Respiratory disease	Restrictive lung disease; obstructive sleep apnoea; obesity hypoventilation syndrome
Endocrine disease	Diabetes mellitus, Cushing's disease, hypothyroidism, infertility
Gastrointestinal disease	Hiatus hernia; gallstones, inguinal hernia
Genitourinary	Menstrual abnormalities, female urinary incontinence; renal calculi
Malignancy	Breast, prostate, colorectal, cervical and endometrial cancer
Musculoskeletal	Osteoarthritis of weight-bearing joints, back pain

Mortality

There is little evidence to suggest that being moderately overweight (actual body weight 110–120% of IBW) carries much excess risk in young adults,[143] but morbidity and mortality rise sharply when BMI is >30 kg m^{-2}, particularly with concomitant cigarette smoking. The risk of premature death doubles in individuals with a BMI of >35 kg m^{-2}.[76] Sudden unexplained death is 13 times more likely in morbidly obese women than in their non-obese counterparts.[63 106] Overweight men participating in the Framingham study[82] had a mortality rate 3.9 times greater than the normal weight group. Morbidly obese individuals are at a much greater risk of mortality from diabetes, cardiorespiratory[62] and cerebrovascular disorders, and certain forms of cancer,[75] as well as a host of other diseases[99 100] (Table 1). These risks are proportional to the duration of obesity;[121] it appears that continued weight gain constitutes a higher risk than for obese individuals whose weight is constant. For a given level of obesity, men are at a higher risk than women,[107] but for both groups weight loss reduces the risk associated with previous obesity. Despite this, weight reduction immediately before surgery has not been shown to reduce perioperative morbidity and mortality.[67 142]

Aetiology

Obesity is a complex and multifactorial disease[150] but, in simple terms, occurs when net energy intake exceeds net energy expenditure over a prolonged period of time. However, it is not always easy to identify a single explanation as to why this occurs in some individuals and not others. The following observations provide some clues:

Genetic predisposition

Obesity tends to be familial, with children of two obese parents having about a 70% chance of becoming obese themselves as compared with a 20% risk for children of non-obese parents. This can, in part, be explained by influences such as diet and lifestyle, but studies of adopted children show weight patterns similar to those of their natural parents, suggesting that a genetic component does exist. Animal studies have confirmed that there is a genetic contribution to obesity. In 1994 the *ob* gene was identified in mice and was shown to control the production of the protein leptin.[21 171] Genetically obese *ob/ob* mice produce insufficient leptin and tend to overeat, leading to obesity. Exogenous leptin reverses hyperphagia and induces weight loss. Clinical studies, however, suggest that only very rarely can such simple genetic defects in leptin production account for significant obesity.[48] In fact, most obese individuals have elevated leptin concentrations, probably a consequence of increased amounts of the source tissue, fat. Furthermore, the rapid increase in the prevalence of obesity over the last 30 years and the fact that the gene pool has remained relatively constant suggest that environmental issues are much more important determinants.

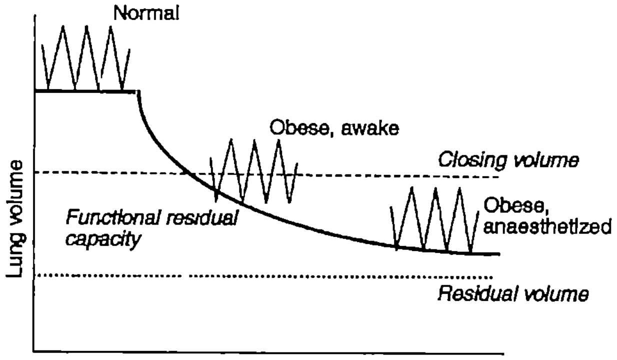

Fig 1 Schematic representation of the effects of severe obesity on functional residual capacity (FRC). Under normal circumstances the FRC (and therefore the tidal excursion) is clear of the closing volume of the lungs. Both anaesthesia and obesity are associated with a reduction in FRC, resulting in airway closure and ventilation/perfusion mismatching during normal tidal ventilation.

Ethnic influences

In the USA there are marked differences in the prevalence of obesity in the different ethnic populations, with African and Mexican Americans being at much higher risk than white Americans. Asian immigrants to the UK have a more central distribution of fat than native Caucasians; this is associated with an increased risk of diabetes and coronary heart disease.[35]

Socioeconomic factors[147]

In the UK there is an inverse relationship between socioeconomic status and the prevalence of obesity, with women of social class I having a 10% risk as compared with 25% in social class V. Of women who move to a higher social class on marriage, only 12% were overweight as compared with 22% who moved to a lower social class.

Medical disorders

Endocrine abnormalities such as Cushing's disease or hypothyroidism predispose to obesity. Patients with such diseases are usually identified quickly from symptoms other than obesity, and appropriate medical therapy normally corrects the problem. In the same way, certain drugs—such as corticosteroids, antidepressants and antihistamines—may also lead to weight gain.

Energy balance

The total number of calories consumed and, particularly, the dietary fat content, is the prime determinant of obesity (the proportion of fat in the UK diet has increased from 20% to 40% over the last 50 years). Alcohol appears to play a key role too, and may influence the site of fat deposition, encouraging central fat to be laid down.

Contrary to popular belief, obese people have a greater energy expenditure than thin people as it takes more energy to maintain their increased body size. Inactivity is usually the result, but not necessarily the cause, of the obesity. However, it has been shown that individuals who remain active in their adult life do best at maintaining healthy weight levels.

While an imbalance between energy intake and energy expenditure is typical of obesity, the daily net calorie excess may be quite modest. For instance, a typical weight gain of 20 kg over 10 years implies an initial daily energy excess of 30–40 kcal, the equivalent of less than half a sandwich.[35]

Distribution of body fat and health risk

It is now becoming clear that it is not only the amount of fat that is important in determining risk, but also its anatomical distribution.[34 88 131] In the central or android type of distribution, which is more common in males, fat is predominantly distributed in the upper body and may be associated with increased deposits of intra-abdominal or visceral fat. In the peripheral or gynaecoid type, fat is more typically distributed around the hips, buttocks or thighs; this is the more usual female pattern of distribution.[20] Central adipose tissue is metabolically more active than fat in the peripheral distribution and is associated with more metabolic complications such as dyslipidaemias, glucose intolerance and diabetes mellitus, and a higher incidence of mortality from ischaemic heart disease.[22 40 131] Morbidly obese patients with a high proportion of visceral fat are also at a greater risk from cardiovascular disease, left ventricular dysfunction and stroke.[136] The mechanism for this increased risk with intra-abdominal fat is not known, but one widely held theory implicates the products of the breakdown of visceral fat being delivered directly into the portal circulation and thereby inducing a significant secondary metabolic imbalance.[121] Although the practical assessment of fat distribution requires sophisticated imaging techniques, the ratio of waist to hip circumference is a useful clinical measure. In European descendants a waist:hip ratio of >1.0 in men and >0.85 in women would tend to suggest a higher proportion of more centrally distributed fat.[34]

Obesity and the respiratory system

Obstructive sleep apnoea

Approximately 5% of morbidly obese patients will have obstructive sleep apnoea OSA, which is characterized by the following features:[10 95 121 169]

(i) Frequent episodes of apnoea or hypopnoea during sleep.[161] An obstructive apnoeic episode is defined as 10 s or more of total cessation of airflow despite continuous respiratory effort against a closed airway. Hypopnoea is defined as 50% reduction in airflow or a reduction sufficient to lead to a 4% decrease in arterial oxygen saturation.[61 121] The number of episodes thought to be clinically significant is often quoted as five or more per hour or >30 per night. The exact numbers are rather arbitrary and it is obviously the clinical sequelae, such as hypoxia, hypercapnia, systemic and pulmonary hypertension and cardiac arrhythmias, that are more important.

(ii) Snoring. This usually gets louder as the airway obstructs, followed by silence, as airflow ceases, and then gasping or choking, as the person rouses and airway patency is restored.

(iii) Daytime symptoms: repeated episodes of fragmented sleep throughout the night causes daytime sleepiness, which is associated with impaired concentration, memory problems and road traffic accidents.[124] The patient may also complain of morning headaches caused by nocturnal carbon dioxide retention and cerebral vasodilation.

(iv) Physiological changes. Recurrent apnoea leads to hypoxaemia, hypercapnia and pulmonary and systemic vasoconstriction. Recurrent hypoxaemia leads to secondary polycythaemia and is associated with an increased risk of ischaemic heart disease and cerebrovascular disease, while hypoxic pulmonary vasoconstriction leads to right ventricular failure.[101 109]

Pathogenesis

Apnoea occurs when the pharyngeal airway collapses during sleep. Pharyngeal patency depends on the action of dilator muscles which prevent upper airway closure. This muscle tone is lost during sleep and, in many individuals, this leads to significant narrowing of the airway, causing turbulent airflow and snoring.[61] Increased inspiratory effort and the response to hypoxia and hypercapnia lead to arousal which, in turn, restores upper airway tone.[51 101] The patient then gasps, takes a few breaths and falls asleep again; the cycle then restarts. Total occlusion can occur if the airway is narrowed further, such as by enlarged pharyngeal soft tissues or by a further reduction in muscle tone by drugs or alcohol.[120]

Risk factors

The main predisposing factors are male gender, middle age and obesity, with other factors such as evening alcohol or night sedation compounding the problem.[61] Other features that help to identify significant OSA are a BMI of >30 kg m^{-2}, hypertension, observed episodes of apnoea during sleep, collar size >16.5, polycythaemia, hypoxaemia/hypercapnia and right ventricular hypertrophy or impairment on electrocardiography and echocardiography.[121] Definitive diagnosis is made by polysomnography in a sleep laboratory.

Obesity hypoventilation syndrome

The acid–base disturbance of OSA, i.e. respiratory acidosis, is initially limited to sleep, with a return to homeostasis during the day. However, a long-term consequence of OSA is an alteration in the control of breathing, the characteristic feature of which is central apnoeic events, that is, episodes of apnoea without respiratory effort. Such episodes, which are associated with a progressive desensitization of the respiratory centres to (nocturnal) hypercapnia, are initially limited to sleep, but eventually lead to type II respiratory failure with an increasing reliance on hypoxic drive for ventilation.[121] At its worst, such obesity hypoventilation culminates in Pickwickian syndrome, which is characterized by obesity, hypersomnolence, hypoxia, hypercapnia, right ventricular failure and polycythaemia.[47]

Airway assessment

A careful and detailed assessment of the morbidly obese patient's upper airway is required before they are anaesthetized. Difficulties with mask ventilation and tracheal intubation may be considerable,[87 112] with the incidence of difficult intubation being quoted at around 13%.[44] These problems are caused by features such as fat face and cheeks, large breasts, short neck, large tongue, excessive palatal and pharyngeal soft tissue, high and anterior larynx, restricted mouth opening and limitation of cervical spine and atlanto-occipital flexion and extension.[40 43]

Preoperative evaluation of the airway must include: (i) assessment of head and neck flexion, extension and lateral rotation; (ii) assessment of jaw mobility and mouth opening; (iii) inspection of oropharnyx and dentition; (iv) checking the patency of the nostrils; (v) inspection of previous anaesthetic charts and questioning the patient about previous difficulties, especially any episodes of upper airway obstruction associated with anaesthesia or surgery (one should always bear in mind that previous records of uneventful anaesthetics may no longer be relevant and new changes, such as further weight gain, pregnancy, head and neck radiotherapy or development of signs and symptoms of upper airway obstruction, must be sought); (vi) a systemic enquiry into features suggestive of obstructive sleep apnoea syndrome, such as excessive snoring with or without episodes of apnoea and daytime hypersomnolence. These imply potential airway obstruction once the patient has been rendered unconscious. These patients are particularly likely to present considerable airway difficulties.

Further imaging of the airway with soft tissue X-rays and CT scans along with consultation with an otolaryngologist for direct or indirect laryngoscopy may provide useful information about the airway if time is available preoperatively. If difficult intubation is envisaged, then an awake fibreoptic intubation should be considered and discussed with the patient.

Obesity and gas exchange

Mass loading of the thoracic and abdominal components of the chest wall in supine, awake obese subjects causes abnormalities of both lung volumes and gas exchange. The well recognized harmful effects of anaesthesia add significantly to the derangement of gas exchange, thereby explaining the problem in gas exchange commonly encountered when anaesthetizing obese patients.

Lung volume

Morbid obesity is associated with reductions in functional residual capacity (FRC), expiratory reserve volume (ERV) and total lung capacity,[32 135] with FRC declining exponentially with increasing BMI.[32] These changes have been attributed to mass loading and splinting of the diaphragm. FRC may be reduced in the upright obese patient to the extent that it falls within the range of the closing capacity with subsequent small airway closure,[83] ventilation–perfusion mismatch, right-to-left shunting and arterial hypoxaemia.[18 86 135 158] Anaesthesia compounds these problems, such that a 50% reduction in observed FRC occurs in the obese anaesthetized patient, as compared with a 20% fall in anaesthetized non-obese subjects[54] (Fig.1). Söderberg and colleagues[148] found an intrapulmonary shunt of 10–25% in anaesthetized obese subjects and 2–5% in lean individuals. FRC can be increased by ventilating with large tidal volumes (e.g. 15–20 ml kg^{-1}) although this has been shown to improve arterial oxygen tension only minimally.[24] In contrast, the addition of positive end-expiratory pressure (PEEP) achieves an improvement in both FRC and arterial oxygen tension but only at the expense of cardiac output and oxygen delivery.[121 127 139] Santesson detailed these perio-

Table 2 Perioperative changes in oxygenation, and the influence of PEEP in patients undergoing bariatric surgery (from reference 139) IPPV = intermittent positive pressure ventilation, PEEP = positive end expiratory pressure, DO_2 = oxygen delivery, Q_T = cardiac output, Q_S/Q_T = stunt fraction, $P(A-a)O_2$ = alveolar arterial oxygen difference

	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	$P(A-a)_{O_2}$ (kPa)	Q_T (litres min^{-1})	Q_S/Q_T (%)	D_{O_2} (ml min^{-1})
Preoperative, air	10.9±1.1	4.6±0.3	3.5±1.1	7.3±1.1	10±4	1346±222
IPPV, zero PEEP, FI_{O_2}=0.5	14.0±2.7	4.5±0.5	28.4±2.6	5.5±1.1	21±5	1039±239
IPPV, 10 cm H_2O PEEP, FI_{O_2}=0.5	15.8±3.0	4.5±0.3	26.7±3.0	5.2±0.9	17±3	996±210
IPPV, 15 cm H_2O PEEP, FI_{O_2}=0.5	21.5±7.2	4.3±0.3	21.2±7.1	4.4±0.6	13±4	862±170

perative changes in oxygenation in patients undergoing bariatric surgery[139] (Table 2). A modest defect in gas exchange and increased shunt fraction preoperatively deteriorate dramatically following induction of anaesthesia and intubation. The addition of PEEP improves oxygenation but leads to reductions in cardiac output and oxygen delivery.

The reduction in FRC impairs the capacity of the obese patient to tolerate periods of apnoea. Obese individuals desaturate rapidly after induction of anaesthesia despite pre-oxygenation. This is a result of having a smaller oxygen reservoir in their reduced FRC and an increase in oxygen consumption.

Usually FRC is reduced as a consequence of a reduction in ERV with residual volume (RV) remaining within normal limits.[135] However, in some obese patients RV is increased suggesting gas trapping and co-existing obstructive airways disease. Forced expiratory volume in 1 s and forced vital capacity are usually within the predicted range, but 6–7% improvements have been demonstrated after weight loss.[81]

Oxygen consumption and carbon dioxide production

Oxygen consumption and carbon dioxide production are increased in the obese as a result of the metabolic activity of the excess fat and the increased workload on supportive tissues.[113] [135] Basal metabolic activity as related to body surface area is usually within normal limits. Normocapnia is maintained usually by an increase in the minute ventilation, which in turn leads to an increased oxygen cost of breathing.[90] However, most obese patients retain the normal response to hypoxaemia and hypercapnia. In exercise, oxygen consumption rises more sharply than in non-obese subjects, which implies respiratory muscle inefficiency.[121]

Gas exchange

Morbidly obese individuals usually have only a modest defect in gas exchange preoperatively with a reduction in Pa_{O_2}[127] and increases in alveolar-to-arterial oxygen difference and shunt fraction. These deteriorate markedly on induction of anaesthesia and high inspired fractions of oxygen are required to maintain adequate arterial oxygen tensions. As previously stated, PEEP improves the Pa_{O_2} but only at the expense of cardiac output and oxygen delivery.[139]

Lung compliance and resistance

Increasing BMI is associated with an exponential decline in respiratory compliance; in severe cases, total compliance can fall to 30% of predicted normal.[129] Although accumulation of fat tissue in and around the chest wall leads to a modest reduction in chest wall compliance, recent work suggests that the decrease in total compliance is principally a consequence of a decrease in lung compliance, this in turn being the result of an increased pulmonary blood volume.[113] [128] Reduced compliance is associated with a decrease in the FRC, encroachment on the closing volume and impairment of gas exchange.[158] [164] Significant obesity is also associated with an increase in total respiratory resistance; once again this is largely a result of an increase in lung resistance.[128] [129] This derangement of lung compliance and resistance results in a shallow and rapid pattern of breathing, increases the work of breathing and limits the maximum ventilatory capacity. As might be anticipated, these changes are even more marked upon assumption of the supine position.

Respiratory efficiency and work of breathing

As implied in the previous section, the combination of increased mechanical pressure from the abdomen, reduction in pulmonary compliance and increase in the metabolic demands of the respiratory musculature result in respiratory muscle inefficiency and an increase in the work of breathing. In normocapnic obese individuals at rest, this may be reflected in a modest 30% increase in the work of breathing, although such respiratory muscle inefficiency may limit the maximum ventilatory capacity and lead to relative hypoventilation at times of high metabolic activity. In the obese individual with established daytime hypoventilation syndrome, work of breathing may approach four times that predicted.

Implications for anaesthesia

Preoperative assessment should include full blood count (to exclude polycythaemia), chest X-ray, supine and upright arterial blood gases, lung function tests and overnight oximetry. Patients with symptoms of significant OSA should be considered for polysomnography and may benefit preoperatively from measures designed to combat nocturnal airway obstruction, such as nocturnal nasal continuous positive airway pressure (CPAP) or bilevel-positive airway pressure (BIPAP).[141] The anaesthetist should also assess the patient's ability to breathe deeply and should check that the nostrils are patent. Specific risks should be explained to the patient, and the possibilities of awake intubation, postoperative ventilation and even tracheostomy discussed.[40]

Tracheal intubation and positive pressure ventilation are mandatory in the morbidly obese patient. The choice between awake and asleep intubation is difficult, and depends upon the anticipated difficulties in a particular patient along with the experience of the anaesthetist.[40] Some authors recommend awake intubation when actual body weight is >175% of IBW.[43] Significant OSA symptoms indicate altered upper airway morphology and make control of bag and mask airway more difficult; some authorities would, therefore, advocate awake intubation in these patients. Another approach is gently to attempt direct laryngoscopy after anaesthetizing the pharynx with local anaesthetic; if the laryngeal structures cannot be visualized, then awake fibreoptic intubation is the safest course of action. Blind nasal intubation has been advocated by some, but should be avoided by all but those very skilled in the technique, as epistaxis and subsequent deterioration in intubating conditions are very real possibilities.

Induction of anaesthesia is likely to be a particularly hazardous time for the patient with an increased risk of difficult or failed intubation.[43 156 167] Bag and mask ventilation is likely to be difficult because of upper airway obstruction and reduced pulmonary compliance. Gastric insufflation during ineffective mask ventilation will further increase the risk of regurgitation and aspiration of stomach contents.

Apart from awake fibreoptic intubation, the safest technique is a rapid sequence induction using succinylcholine following a period of adequate preoxygenation. It is essential to have skilled anaesthetic assistance together with adequate numbers of staff in order to turn the patient should the need arise. A full range of aids for a difficult intubation should be available, and should include short-handled, polio blade and McCoy laryngoscopes, a gum elastic bougie and standard and intubating laryngeal mask airways. Equipment for cricothyroidotomy and transtracheal ventilation should also be available. Correct position of the tracheal tube must be confirmed by both auscultation and capnography. It is highly desirable to have the services of another experienced anaesthetist throughout the induction period rather than having to wait for assistance if difficulty is encountered.

Periods of hypoxaemia and hypercapnia may increase pulmonary vascular resistance and precipitate right heart failure. Obese patients should not be allowed to breathe spontaneously under anaesthesia, as hypoventilation is likely to occur, with consequent hypoxia and hypercapnia. Further respiratory embarrassment will occur if the patient is placed in the lithotomy or Trendelenburg position and these should be avoided if at all possible.[121 138] The obese patient will require mechanical ventilation with high inspired oxygen fractions, possibly with the addition of PEEP to maintain an adequate arterial oxygen tension; a ventilator of sufficient power and sophistication is, therefore, required. End-tidal capnography is a poor guide to adequacy of ventilation in the obese patient because of the alveolar-to-arterial difference in carbon dioxide in these patients. Instead, serial arterial blood gas analysis should be used to assess adequacy of minute ventilation.

Pulmonary complications are more common in obese patients,[125 148 156] but BMI and preoperative lung function tests are not accurate predictors of postoperative problems.[142] Obese patients may be more sensitive to the effects of sedative drugs, opioid analgesics and anaesthetic drugs, so they may benefit from a period of postoperative ventilation to allow safe elimination of residual anaesthetic or sedative agents. Although technically challenging, regional anaesthetic techniques, such as peripheral nerve and thoracolumbar epidural blockade, may help to attenuate many of these problems.[134] Postoperative ventilation is more likely to be required in obese patients who have coexisting cardiorespiratory disease or carbon dioxide retention and in those who have undergone prolonged procedures or who have developed pyrexia after the operation.[52]

The trachea should only be extubated when the patient is fully awake and transferred to the recovery room sitting up at 45°.[160] Humidified supplemental oxygen should be administered immediately, and chest physiotherapy commenced soon after the operation. Some obese patients, particularly those with a history of OSA, may benefit from nocturnal nasal CPAP. Episodes of OSA are most frequent during rapid eye movement (REM) sleep, the extent of which is relatively low in the initial postoperative period, but in excess on the third to fifth postoperative nights.[121] The hazards of OSA may, therefore, be at their worst some days after surgery; this has obvious implications for the duration of postoperative oximetry and oxygen therapy.

Obesity and the cardiovascular system

Cardiovascular disease dominates the morbidity and mortality in obesity and manifests itself in the form of ischaemic heart disease, hypertension and cardiac failure. A recent Scottish health survey found the prevalence of any cardiovascular disease was 37% in adults with a BMI of >30 kg m^{-2}, 21% in those with a BMI of 25–30 kg m^{-2} and only 10% in those with a BMI of <25 kg m^{-2}.[111] All morbidly obese patients presenting for anaesthesia should be investigated extensively for cardiovascular complications preoperatively and certain patients should be referred to a cardiologist for further optimization.

Cardiovascular derangement

Hypertension

Mild to moderate hypertension is seen in 50–60% of obese patients and severe hypertension in 5–10%,[7] with a 3–4 mm

Hg increase in systolic and a 2 mm Hg increase in diastolic arterial pressure for every 10 kg of weight gained.[33] An expansion of the extracellular volume, resulting in hypervolaemia, and an increase in cardiac output are characteristic of obesity-induced hypertension. The exact mechanism for hypertension in the obese is not known, and probably represents an interaction between genetic, hormonal, renal and haemodynamic factors. Hyperinsulinaemia, which is characteristic of obesity, can contribute by activating the sympathetic nervous system and by causing sodium retention. In addition, insulin resistance may be responsible for the enhancement in pressor activity of norepinephrine and angiotensin II.[119]

Hypertension *per se* leads to concentric left ventricular hypertrophy and a progressively non-compliant left ventricle which, when added to the increased blood volume, increases the risk of cardiac failure.[12–14 16 121]

Weight loss has been shown to reduce hypertension in the obese.[8 14 19 26 71 105]

Ischaemic heart disease

It is now generally accepted that obesity is an independent risk factor for ischaemic heart disease[63 89 100] and is more common in those obese individuals with a central distribution of fat.[10] Other factors such as hypertension, diabetes mellitus, hypercholesterolaemia and reduced high density lipoprotein levels, which are all common in the obese, will compound the problem.[116] Interestingly, 40% of obese patients with angina do not have demonstrable coronary artery disease;[111] in other words, angina may be a direct symptom of obesity.

Blood volume

Total blood volume is increased in the obese but on a volume/weight basis is less than that in non-obese individuals (50 ml kg^{-1} compared with 75 ml kg^{-1}),[23] with most of this extra volume being distributed to the fat organ.[6] Splanchnic blood flow is increased by 20% whereas renal and cerebral blood flow are normal.[9]

Cardiac arrhythmias

Arrhythmias may be precipitated in the obese by a number of factors: hypoxia, hypercapnia, electrolyte disturbance caused by diuretic therapy, coronary artery disease, increased circulating catecholamine concentrations, OSA, myocardial hypertrophy and fatty infiltration of the conduction system.[30 89 113 142 154]

Cardiac function

The morbidly obese individual is at risk of a specific form of obesity-induced cardiac dysfunction, although the belief that this is secondary to fatty infiltration of the heart ('cor adiposum') is no longer valid.[6 17] Autopsy studies have shown that, although increases in epicardial fat are common, fatty infiltration of the myocardium is uncommon and seems to affect mainly the right ventricle, the latter possibly being associated with conduction abnormalities and arrhythmias.[17] There is a linear relationship between cardiac weight and body weight up to 105 kg, after which cardiac weight continues to increase, but at a slower rate.[63 144] The increase in heart weight is a consequence of dilation and eccentric hypertrophy of the left and, to a lesser extent, the right ventricle.[63 165]

Otherwise healthy obese individuals demonstrate an increased cardiac output, elevated left ventricular end-diastolic pressure (LVEDP) and left ventricular hypertrophy on echocardiography. Left ventricle systolic function is also impaired,[4 13] especially during exercise, when the ejection fraction rises to a lesser extent, and more slowly, than in lean individuals.[5 11 68]

The pathophysiology of obesity-induced cardiomyopathy is now well defined,[10 63 121] largely as a result of studies in non-hypertensive individuals awaiting bariatric surgery (of some importance since the general morbidly obese population may be somewhat less fit then this preselected group). Figure 2 outlines the aetiology of obesity cardiomyopathy and its interaction with hypertension, ischaemic heart disease and respiratory disease. Obesity is associated with an increase in blood volume[9] and cardiac output,[10] the latter rising by 20–30 ml per kilogram of excess body fat. The increase in cardiac output is largely a result of ventricular dilation and an increase in stroke volume.[7 10] The ventricular dilation results in increased left ventricle wall stress, leading to hypertrophy.[10 17 118] Such eccentric left ventricular hypertrophy results in reduced compliance and left ventricular diastolic function, i.e. impairment of ventricular filling, leading to elevated LVEDP and pulmonary oedema.[10 13 16 29 57 58] The capacity of the dilated ventricle to hypertrophy is limited so, when left ventricular wall thickening fails to keep pace with dilation, systolic dysfunction ensues ('obesity cardiomyopathy').[10 14 16 89 98] The problem is often compounded by superimposed hypertension and ischaemic heart disease. Ventricular hypertrophy and dysfunction worsen with increasing duration of obesity and improve to some extent with weight loss.[5 8 12 14 15]

The morbidly obese tolerate exercise badly[11] with any increase in cardiac output being achieved by increasing the heart rate, without an increase in stroke volume or ejection fraction. This is often accompanied by an increase in the filling pressures.[7] In the same way, changing position from sitting to supine is associated with significant increases in cardiac output, pulmonary capillary wedge pressure and mean pulmonary artery pressure, together with reductions in heart rate and peripheral resistance.[126]

Clinical features

Morbidly obese subjects often have very limited mobility and may, therefore, appear to be asymptomatic even when they have significant cardiovascular disease. Symptoms

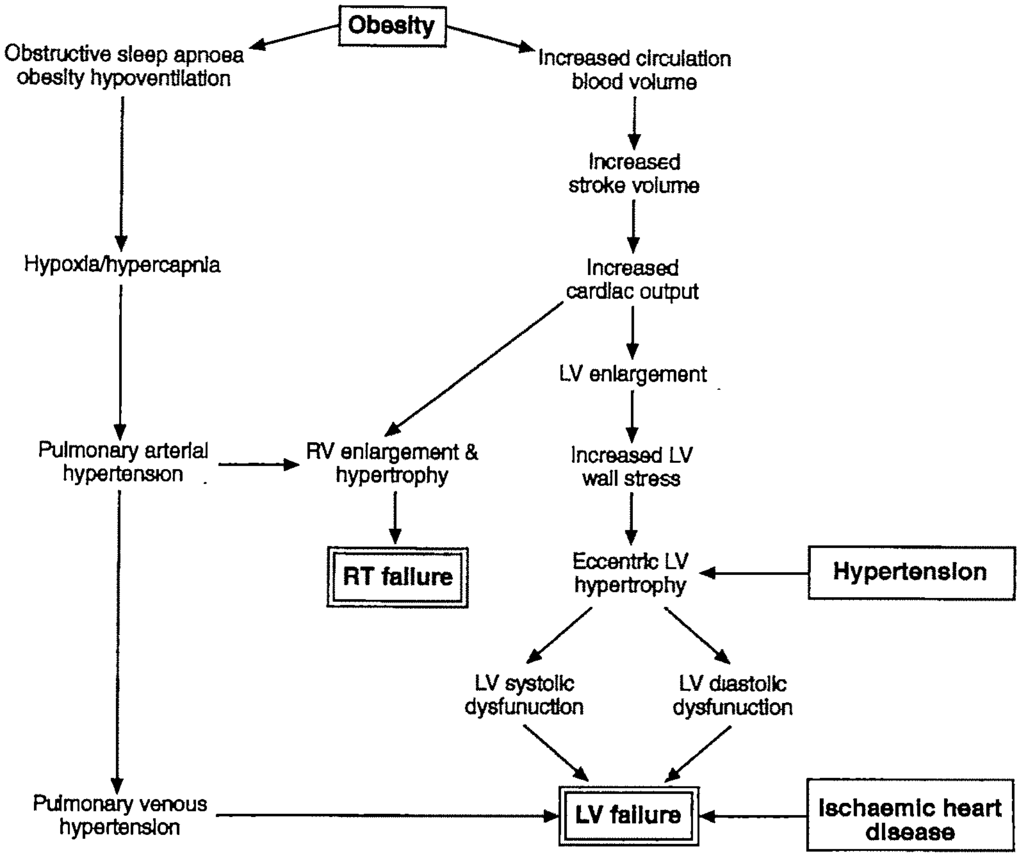

Fig 2 The aetiology of obesity cardiomyopathy, and its association with right-sided heart failure, systemic hypertension and ischaemic heart disease. LV, left ventricular; RV, right ventricular

such as angina or exertional dyspnoea may occur only very occasionally, but actually coincide with most periods of significant physical activity. Many individuals will prefer to sleep upright in a chair, and therefore deny the symptoms of orthopnoea and paroxysmal nocturnal dyspnoea. Asking the patient to walk the length of the ward may reveal a markedly reduced exercise tolerance, and assuming the supine position may produce significant orthopnoea and even cardiac arrest.[153] The patient should have a detailed and thorough cardiovascular examination, looking in particular for evidence of hypertension (with an appropriately sized blood pressure cuff) and cardiac failure. Signs of cardiac failure, such as raised jugular venous pressure, added heart sounds, pulmonary crackles, hepatomegaly and peripheral oedema, may all be difficult to elicit in the morbidly obese subject, and investigations are indicated.

Investigations

An electrocardiogram is mandatory preoperatively. It may be of low voltage because of the excess overlying tissue and as such might underestimate the severity of ventricular hypertrophy. Axis deviation and atrial tachyarrhythmias are relatively common. Chest radiography may reveal cardiomegaly suggestive of cardiac failure, but is often normal. Echocardiography may be difficult, but can provide useful information, with eccentric left ventricular hypertrophy suggesting significant obesity-induced changes even if ventricular function appears normal. Transoesophageal echocardiography may provide better images, especially of the left side of the heart, although is obviously more invasive. Testing of exercise tolerance is likely to be impossible if coronary artery disease is suspected. If time is available, the patient should be referred to a cardiologist for further investigation and optimization, such as control of blood pressure, treatment of heart failure or coronary angioplasty.

Anaesthetic implications

In the presence of respiratory disease, ventricular impairment is almost inevitable, but its severity may be underestimated by clinical evaluation. Rapid weight gain preoperatively may indicate worsening cardiac failure, although weight gain once a person has been accepted for bariatric surgery is well recognized.[59 140] Intraoperative ventricular failure may occur for a variety of reasons, including rapid intravenous fluid administration (indicating left ventricular diastolic dysfunction), negative inotropy of anaesthetic agents or pulmonary hypertension precipitated by hypoxia or hypercapnia. The anaesthetist should always have a selection of inotropes and vasodilators to hand.

Cardiac performance is likely to deteriorate following induction of anaesthesia and tracheal intubation in the obese patient.[4] In one study of obese individuals undergoing abdominal surgery, cardiac index fell by 17–33% after induction and intubation, compared with a fall of 4–11% in lean controls. This derangement persisted postoperatively, with the cardiac index 13–23% less than preoperative control values in the obese group, whereas in lean controls cardiac performance returned to normal.[4]

An arterial line will allow accurate monitoring of arterial pressure and regular blood gas analysis. Central venous pressure monitoring is desirable as it allows some assessment of cardiac function and can be used for inotrope infusions in case of deteriorating cardiac performance.[44] Patients with documented cardiac failure may benefit from the use of a pulmonary artery flotation catheter.

Practical considerations

Premedication

Opioid and sedative drugs may cause respiratory depression in the morbidly obese[156] and are probably best avoided, although one study failed to demonstrate an increased risk of oxyhaemoglobin desaturation with benzodiazepines.[31] The intramuscular and subcutaneous routes should be avoided, since absorption is very unreliable.[52 156] If awake fibreoptic intubation is being considered, then an antisialogogue may be appropriate.

All morbidly obese patients should receive prophylaxis against acid aspiration even if they do not declare any symptoms of heartburn or reflux.[44 52 156 162] A combination of an H_2 blocker (e.g. ranitidine 150 mg orally) and a prokinetic (e.g. metoclopramide 10 mg orally) given 12 h and 2 h before surgery will reduce the risk of aspiration pneumonitis. Some anaesthetists also advocate giving 30 ml of 0.3 M citrate immediately before induction as an extra precaution.

Most of the patient's usual medications, such as cardiovascular drugs and steroids, should be continued as normal until the time of surgery, although it is recommended that angiotensin converting enzyme inhibitors be stopped on the day before surgery as their continuation can lead to profound hypotension during anaesthesia.

If the patient is diabetic, a dextrose–insulin regimen will be required for all but the shortest procedures. Insulin requirements are likely to increase postoperatively. Expert advice from a diabetologist may be helpful.

Morbidly obese patients are more likely to be immobile postoperatively and are at increased risk of deep-vein thrombosis. Low-dose subcutaneous heparin should be given as prophylaxis and continued into the postoperative phase until the patient is fully mobile. Other antiembolic measures, such as pneumatic leggings or graded compression stockings, should be used wherever possible but may be difficult to fit in larger patients.

This group of patients is also at increased risk of postoperative wound infection and may require prophylactic antibiotics. This should be discussed with the surgeon and also a microbiologist if appropriate.

Positioning and transfer

Most operating tables are designed for patients of up to 120–140 kg in weight. Exceeding this limit may put the patient and staff at risk. Specially designed tables may be required, or two normal tables may be placed side by side.[52]

The patient should be anaesthetized on the operating table in the operating theatre to avoid unnecessary transfer from the anaesthetic room and the associated risks to both patient and staff. Once the patient is in position, particular care should be paid to protecting pressure areas, as the risk of pressure sores and neural injuries[96] is greater in the obese. Compression of the inferior vena cava must be avoided by left lateral tilt of the operating table or by placing a wedge under the patient. Some obese patients are best positioned in the lateral decubitus position so as to reduce the amount of weight loading on the chest.

Transfer of the obese patient around the hospital is probably best done on their own hospital bed, as normal theatre trolleys are likely to be inadequate for the purpose. Appropriate manpower should always be available when moving morbidly obese patients and local lifting policies should be adhered to.

Intravenous access

This may be a problem because of excessive subcutaneous tissue. Many anaesthetists would advocate establishing central venous access, but this in itself can be difficult. Use of portable ultrasound equipment may improve success.

Monitoring

Invasive arterial pressure monitoring has been advocated for all but the most minor procedures in the morbidly obese.[44 52] If a non-invasive cuff is to be used, it should be of an appropriate size, as standard cuffs will tend to over-estimate the arterial pressure. Pulse oximetry, electrocardiography, capnography and monitoring of neuromuscular block are all mandatory. Use of central venous and pulmonary artery flotation catheters should be considered in patients undergoing extensive surgery or those with serious cardiorespiratory disease.

Regional anaesthesia

The use of regional anaesthesia in the obese reduces the risks from difficult intubation and acid aspiration and also provides safer and more effective postoperative analgesia.[142] For thoracic and abdominal procedures, most anaesthetists advocate the use of combined epidural and general anaesthesia. This has advantages over general anaesthesia alone, including reduced opioid and potent inhalational anaesthetic requirements,[44 72] earlier tracheal extubation,[77 156] reduced postoperative pulmonary complications[44 72] and improved postoperative analgesia, allowing more rigorous physiotherapy and a better cough.[134]

Regional anaesthesia in the obese can be technically challenging because of difficulties in identifying the usual bony landmarks. Epidural and spinal anaesthesia may be made easier by sitting the patient upright and by using longer needles.[44] Ultrasound has been successfully used in the obese to identify the epidural space and to guide the Tuohy needle into position.[163] Some anaesthetists would advocate the siting of epidural catheters on the evening before surgery to save time the next day, and also to allow heparin prophylaxis to be given on the morning of surgery. In the same way, peripheral nerve blockade may be made easier and safer by the use of insulated needles and a nerve stimulator.[64]

Local anaesthetic requirements for epidural and spinal anaesthesia are reduced to 75–80% of normal in the morbidly obese, since fatty infiltration and the increased blood volume caused by increased intra-abdominal pressure reduce the volume of the epidural space.[44 151] This can lead to an unpredictable spread of local anaesthetic and variability in block height.[85 132] Blocks extending above T_5 risk respiratory compromise, and cardiovascular collapse secondary to autonomic blockade.[123] For these reasons, the anaesthetist must always be prepared to convert to general anaesthesia and have the necessary equipment and assistance immediately to hand.

Systemic analgesia

The use of opioid analgesics may be hazardous in the obese. The intramuscular route is not recommended as it is unpredictable and has been shown to provide poorer analgesia than other routes.[41 134] If the intravenous route is to be used, then a patient-controlled analgesia system (PCAS) is probably the best option.[25] PCAS has been shown to provide effective analgesia in the obese, although respiratory depression has been reported.[155] Doses should be based on IBW.[142] Supplemental oxygen and close observation, including pulse oximetry monitoring, are recommended.

Postoperative epidural analgesia, using opioids or local anaesthetic solutions, may provide the most effective and safest analgesia for the obese patient.[142] The epidural route for opioid administration is preferred over other routes because it produces less drowsiness, nausea and respiratory depression, earlier normalization of bowel motility, improved pulmonary function and reduced hospital stay.[41 72 134] As a result of the potential for delayed onset respiratory depression, supplemental parenteral opioids should probably be avoided. Continuous epidural analgesia with local anaesthetics has been shown to have a beneficial effect on cardiovascular function, with a reduction in left ventricular stroke work,[77] although an associated motor block will delay ambulation.

All of the above regimens can be supplemented with oral analgesics such as paracetamol or non-steroidal anti-inflammatory drugs if appropriate.

Considerations in obstetrics

The obese pregnant patient presents particular difficulties, which include: (i) increased risk of chronic hypertension, pre-eclampsia and diabetes;[3 87] (ii) higher incidence of difficult labour with increased likelihood of instrumental delivery and Caesarean section;[87 132] (iii) Caesarean section operations tend to be longer[130] with a higher incidence of postoperative complications, including greater blood loss, deep-vein thrombosis and wound infection or dehiscence;[87] (iv) increased risk of anaesthesia-related morbidity and mortality during Caesarean section and in particular, increased risk of failed intubation and gastric aspiration during procedures under general anaesthesia;[87] (v) increased incidence of multiple, failed attempts at epidural siting;[87 132] (vi) increased risk of fetal morbidity and mortality, with some studies showing an increased incidence of fetal distress;[87] (vii) supine and Trendelenburg positions further reduce FRC, increasing the possibility of hypoxaemia; (viii) some studies show a greater cephalad spread of local anaesthetic during spinal and epidural anaesthesia;[84] (ix) loss of intercostal muscle function during spinal anaesthesia leading to respiratory difficulty; (x) possible severe reduction in cardiac output with general anaesthesia, related to profound aorto-caval compression and the use of PEEP.

Solutions

If at all possible, general anaesthesia should be avoided in the pregnant obese patient. If it is absolutely essential, then a difficult intubation should be anticipated and the appropriate assistance and equipment made readily available. If time is available, an awake fibreoptic intubation should be considered. A clear action plan must have been formulated for the possibility of a failed intubation. The mother's safety must come first; if a failed intubation is deemed likely, then a rapid sequence induction should not be considered.

Siting an epidural catheter early in labour allows the anaesthetist to establish good analgesia in a calm and controlled atmosphere rather than having to rush in the event of an emergency situation.[87] Epidural analgesia can be supplemented for operative procedures and may reduce the likelihood of post-partum deep-vein thrombosis.

'Single-shot' spinal anaesthesia may be inadequate for a prolonged Caesarean section, so consideration should be given to a combined spinal–epidural technique if a subarachnoid block is favoured. Local anaesthetic requirements may be reduced by up to 25% in the obese pregnant state.

Anaesthesia and the obese child

Overweight children become obese adults. It appears that body fat distribution is more important than percentage body fat in determining cardiovascular risk factors for later life.[55 73] In a 57 yr follow-up study, all-cause and cardiovascular mortality was greater for adults who had had a higher childhood BMI.[80 92]

The child with Prader–Willi syndrome is likely to present a particular challenge to the anaesthetist.[56] Features of the syndrome include hypotonia, mental retardation, obesity, diabetes mellitus, scoliosis and sleep apnoea (which may worsen postoperatively). Cardiovascular disturbance (hypertension, arrhythmias), restrictive pulmonary defects and thermoregulatory abnormalities have also been described. It would seem prudent that these children should be anaesthetized in specialist centres that have experience of the condition.

Laparoscopic procedures in the obese

Despite the expected diaphragmatic splinting and reduction in FRC, obese patients seem to tolerate laparoscopic procedures relatively well. Dumont and colleagues[64] studied the respiratory mechanics and arterial blood gases in 15 morbidly obese patients undergoing laparoscopic gastroplasty. They showed that abdominal insufflation to 2.26 kPa led to a 31% decrease in respiratory compliance, increases of 17% and 32% in peak and plateau airway pressures (at constant tidal volume), significant hypercapnia but no change in arterial oxygen saturation. Pulmonary compliance and insufflation pressures returned to baseline values after abdominal deflation and the procedures were well tolerated. Similarly, Juvin and colleagues[97] demonstrated that obese patients undergoing laparoscopic gastroplasty had significantly reduced analgesic requirements, were able to walk sooner and had a shorter hospital stay than a comparable group of patients who had had an open procedure. Laparoscopy for gastroplasty may improve the immediate postoperative course but the anaesthetist must be aware that Trendelenburg and reverse Trendelenburg positions are likely to be poorly tolerated and that hypercarbia may cause arrhythmias and cardiovascular instability during the procedure.

Obesity and gastrointestinal disorders

It is commonly believed that combination of increased intra-abdominal pressure, high volume and low pH of gastric contents,[159] delayed gastric emptying and an increased incidence of hiatus hernia and gastro-oesophageal reflux place the obese patient at a higher risk of aspiration of gastric content followed by aspiration pneumonitis. Recent studies, however, have challenged this contention. Zacchi and colleagues[170] showed that obese patients without symptoms of gastro-oesophageal reflux have a resistance gradient between the stomach and the gastro-oesophageal junction similar to that in non-obese subjects in both the lying and sitting positions. Although obese individuals have a 75% greater gastric volume than normal individuals, recent work has shown that gastric emptying is actually faster in the obese, especially with high-energy content intake such as fatty emulsions. However, as a result of the larger gastric volume, the residual volume is larger in obese individuals.[168] Both the faster gastric emptying and the larger gastric volume can be partially reversed by weight loss.[152] Despite such conflicting evidence, it is sensible to take precautions against acid aspiration. This includes the use of H_2 receptor antagonists,[162] antacids and prokinetics; rapid sequence induction with cricoid pressure and tracheal extubation with the patient fully awake.[121]

Diabetes mellitus

Obesity is an important independent risk factor for type II or maturity-onset diabetes mellitus. Some studies show a >10% incidence of an abnormal glucose tolerance test in patients undergoing bariatric surgery.[121] All obese patients should have a random blood sugar test performed preoperatively and, if indicated, a glucose tolerance test. The catabolic response to surgery may necessitate the use of insulin postoperatively to control glucose concentrations. Failure to control blood glucose concentrations adequately will render the patient more susceptible to wound infections and will increase the risk of myocardial infarction during periods of myocardial ischaemia.[133]

Thromboembolic disease

The risk of deep-vein thrombosis in obese patients undergoing non-malignant abdominal surgery is approximately twice that of lean patients (48% *vs* 23%), with a similar increased risk of pulmonary embolus.[50 121] It is the commonest complication of bariatric surgery, with the incidence reported to be between 2.4% and 4.5%.[60 66 121] The increased risk of thromboembolic disease in obese patients is likely to result from prolonged immobilization leading to venous stasis, polycythaemia, increased abdominal pressure with increased pressure in the deep venous channels of the lower limb, cardiac failure and decreased fibrinolytic activity with increased fibrinogen concentrations. Measures to prevent venous thromboembolism should always be taken.

Drug handling in obesity

The physiological changes associated with obesity lead to alterations in the distribution, binding and elimination of many drugs.[1 2 115] The net phamacokinetic effect in any patient is often uncertain, making monitoring of clinical end-points (such as heart rate, arterial pressure and sedation) and serum concentrations of drugs more important than empirical drug dosing based on published data.[115 142] For drugs with narrow therapeutic indices (e.g. aminophylline, aminoglycosides or digoxin), toxic reactions may occur if patients are dosed according to their actual body weight.[1 2 49 115]

Absorption

Oral absorption of drugs remains essentially unchanged in the obese patient.[49]

Volume of distribution

Factors that affect the apparent volume of distribution (V_d) of a drug in the obese include the size of the fat organ, increased lean body mass, increased blood volume and cardiac output, reduced total body water, alterations in plasma protein binding and the lipophilicity of the drug.[36] Thiopental, for instance, has an increased V_d because of its highly lipophilic nature and also because of the increased blood volume, cardiac output and muscle mass.[117] Therefore the absolute dose should be increased, even though on a weight-for-weight basis the dose required will be less than that for a lean individual. An increase in the volume of distribution will reduce the elimination half-life unless the clearance is increased.[1 2] With thiopental and other lipophilic drugs (such as benzodiazepines or potent inhalational anaesthetic agents), effects may persist for some time after discontinuation.

There may be variable effects of obesity on the protein binding of some drugs. The increased concentrations of triglycerides, lipoproteins, cholesterol and free fatty acids may inhibit protein binding of some drugs, and so increase free plasma concentrations.[166] In contrast, increased concentrations of α_1 acid glycoprotein may increase the degree of protein binding of other drugs (e.g. local anaesthetics), so reducing the free plasma fraction.

Elimination

Although histological abnormalities of the liver are relatively common, hepatic clearance is usually not reduced in the obese. Phase I reactions (oxidation, reduction and hydrolysis) are usually normal or increased in obesity, whereas metabolism of some drugs by phase II reactions (e.g. lorazepam) is consistently increased. Cardiac failure and reduced liver blood flow may slow the elimination of drugs that are rapidly eliminated by the liver (e.g. midazolam or lidocaine).[115]

Renal clearance increases in obesity because of the increased renal blood flow and glomerular filtration rate.[115] In obese patients with renal dysfunction, estimates of the creatinine clearance from standard formulae tend to be inaccurate and dosing regimens for renally excreted drugs should be based instead on measured creatinine clearance.[146]

Inhalational anaesthetics

The traditional theory that slow emergence from anaesthesia in morbidly obese patients is a result of delayed release of volatile agent from excessive adipose tissue has been challenged.[108] Reductions in blood flow to the fat organ may limit the delivery of volatile agents to fat stores, with the slow emergence more probably resulting from increased central sensitivity. In fact, some studies demonstrate comparable recovery times in obese and lean subjects for anaesthesia lasting 2–4 h.[53]

Obese patients may be more susceptible to the ill-effects of altered hepatic metabolism of volatile agents. Plasma concentrations of bromide, a marker of reductive and oxidative metabolism of halothane, are increased in obese patients.[121] Increased reductive metabolism may be an important factor in the development of liver injury after exposure to halothane, and this may be more likely in obese individuals at risk from hypoxaemia and reduced liver blood flow. Concentrations of inorganic free fluoride ions are higher in obese patients following exposure to halothane or enflurane, increasing the risk of nephrotoxicity.[27 28] This does not appear to be the case with sevoflurane, despite its significant hepatic metabolism.[74] Fluoride concentrations are not significantly increased after isoflurane anaesthesia,[149] so this remains the inhalational agent of choice for many anaesthetists. Although its rapid elimination and analgesic properties render nitrous oxide potentially attractive, its usefulness is limited by the high oxygen demands of many morbidly obese patients. The influence of obesity on the pharmacokinetics of commonly used anaesthetic drugs is summarized in Table 3.

Trauma and the obese patient

It is a widely held belief that the outcome of trauma in obese patients is poor, but data to support this are scarce. Boulanger and colleagues examined retrospectively the pattern of blunt trauma in obese and non-obese individuals over a 4 yr period.[37] The obese group tended to be involved more in car crashes (62.7% *vs* 54.1%) and to have better GCS scores, and they were more likely to have rib fractures, pulmonary contusions, pelvic fractures and extremity fractures. They were less likely to have suffered head trauma or liver injuries. Smith-Choban and colleagues reported an eight-fold increase in mortality following blunt trauma in morbidly obese patients compared with the non-obese.[145]

The metabolic response to severe trauma appears to be different in obese and non-obese subjects. Jeevanandam and colleagues[93] showed that traumatized obese patients mobilized relatively more protein and less fat than non-obese victims. In other words, they were unable to use their most abundant fuel source. They suggest that the nutritional management of obese trauma victims should provide enough glucose calories to spare protein.

Care of the morbidly obese trauma victim in the resuscitation room is likely to prove difficult. Given the high probability of underlying cardiorespiratory impairment, such patients are likely to require high inspired oxygen fractions, early intubation and respiratory support, meticulous fluid resuscitation with invasive monitoring, and adequate personnel to transport them around the emergency

Table 3 Influence of obesity on the pharmacokinetics of anaesthetic drugs (adapted from reference 143). TBW=total body weight, LBW=lean body weight, MAC = minimum alveolar concentration

Drug	Altered pharmacokinetics	Clinical implications
Hypnotics		
Thiopental	Increased central volume of distribution, prolonged elimination half-life	Increased absolute dose; reduced dose per unit body weight, prolonged duration of action
Propofol	Little known	Increased absolute dose, reduced dose per unit body weight
Midazolam, diazepam	Central volume of distribution increases in line with body weight, prolonged elimination half-life	Increased absolute dose, same dose per unit body weight, prolonged duration of action, particularly after infusion
Neuromuscular blocking drugs		
Succinylcholine	Plasma cholinesterase activity increases in proportion to body weight	Increased absolute dose, reduced dose per unit body weight, doses of 120–140 mg appear satisfactory
Atracurium	No change in absolute clearance, absolute volume of distribution and absolute elimination half-life	Unchanged dose per unit body weight
Vecuronium	Impaired hepatic clearance and increased volume of distribution lead to delayed recovery time	Give according to estimated lean body weight
Pancuronium	Low lipid solubility	Unchanged dose per unit body weight
Dimethyl tubocurarine	Elimination half-life increases in proportion with % obesity	Give according to estimated LBW
Opioids		
Fentanyl	No change in elimination following $10\ \mu g\ kg^{-1}$	Dose per unit body weight unchanged
Alfentanil	Elimination may be prolonged	Adjust dose to LBW
Morphine	No information available	
Local anaesthetics		
Lidocaine	Increased absolute V_D, unchanged V_D adjusted for body weight; increased epidural fat content and epidural venous engorgement	I v. dose unchanged dose per unit body weight; extradural dose. 75% of dose calculated according to TBW
Bupivacaine	No information available	High segmental level following subarachnoid blockade
Inhalational anaesthetics		
Nitrous oxide	Little information	Increased $F\text{I}_{O_2}$ limits practical usefulness; intestinal distension may contribute to perioperative difficulties
Halothane	Considerable deposition in adipose tissue; increased risk of reductive hepatic metabolism	Possible increased risk of halothane hepatitis
Enflurane	Blood gas partition coefficient falls with increasing obesity, inorganic fluoride concentrations rise twice as fast in obese individuals	Possibly lower MAC, increased risk of fluoride nephrotoxicity following prolonged administration
Sevoflurane	No difference in fluoride concentrations between obese and non-obese patients	

department. Bleeding is likely to produce early cardiovascular decompensation and so should be vigorously sought and treated. Portable radiographs may be of poor quality because of overlying soft tissue, and clinical signs may be difficult to elicit. More sophisticated imaging techniques, such as CT scanning, may be needed, although many CT tables have weight restrictions of about 160 kg. The attending physician should always consider the possibility of covert pathology in the obese trauma patient.

The obese patient on the intensive care unit

Few data are available on the morbidity and mortality of obese patients in the intensive care setting, but again it is widely held that the outcome is poor. Despite this, morbid obesity was not included as a comorbid variable in the development of the APACHE (acute physiology and chronic health evaluation) II and III prognostic indices.[103] [104] Obese patients are more likely to be admitted to the intensive care unit. Rose and colleagues reported that acute postoperative pulmonary events were twice as likely in the obese as in the non-obese, and that hospitalized obese patients were at an increased risk of developing respiratory complications.[137]

The alterations in pulmonary function that have already been outlined are important when considering mechanical ventilation in the obese patient. A tidal volume based on the patient's actual body weight is likely to produce alveolar over-distension and high airway pressure, so increasing the risk of barotrauma. An initial tidal volume based on IBW should be used which can then be adjusted according to inflation pressures and blood gas analysis.[115] The use of PEEP may help to prevent airway closure and atelectasis but may be at the expense of the cardiac output. Weaning from mechanical ventilation may be difficult because of high oxygen requirements, increased work of breathing, reduced lung volumes and ventilation–perfusion mismatching. Burns and colleagues[46] showed that a position of 45° head-up tilt resulted in a larger tidal volume and a lower respiratory rate than either the 0° or 90° position, and so may be of benefit during weaning. If a long stay in the ICU is envisaged, early tracheostomy may assist weaning, although the percutaneous approach is likely to prove difficult. One must always consider the possibility of the obese patient requiring emergency re-intubation and so extubation should be planned when adequate personnel are available, especially if the initial intubation was problematic.

The morbidly obese patient is likely to have significant cardiovascular impairment and to tolerate fluid loading poorly. Invasive haemodynamic monitoring may assist in titrating fluid replacement and assessing cardiac performance. Siting of central venous catheters may be difficult, resulting in a higher incidence of catheter misplacement and local complications such as infection and thrombosis.[38] Femoral vein catheterization may be impossible owing to local intertrigo. Doppler ultrasound has been shown to improve the success rate of central vein cannulation in high-risk groups with a reduced rate of complications.[78, 79]

Despite having excess body fat stores and an increased lean body mass, obese individuals are at risk from developing protein malnutrition during periods of metabolic stress.[91] Weight reduction during episodes of critical illness is not beneficial and appropriate nutritional support should not be withheld. Obese individuals are not able to mobilize their fat stores during critical illness and tend to rely on carbohydrate instead. The increased carbohydrate use increases the respiratory quotient and accelerates protein breakdown further to fuel gluconeogenesis.[93] Energy expenditure equations tend to be unreliable in critical illness, especially in the obese.[94] An indirect calorimeter should be used to calculate energy expenditure,[114] but if one is not available, then patients should receive 20–30 kcal kg^{-1} of IBW per day. Most of the calories should be given as carbohydrate, with fats given to prevent essential fatty acid deficiency. Protein requirements may be difficult to assess because of an increased lean body mass, but 1.5–2.0 g kg^{-1} of IBW should achieve nitrogen balance.[45, 91] Expert advice should be sought from a dietician.

Clearly the morbidly obese patient will present the emergency room and intensive care staff with a formidable challenge. Better understanding of the pathophysiology and complications that accompany obesity may improve their care and outcome. More research on the outcome of the morbidly obese in these settings is required.

References

1 Abernethy DR, Greenblatt DJ. Pharmacokinetics of drugs in obesity. *Clin Pharmacokinet* 1982; **7**: 108–24

2 Abernethy DR, Greenblatt DJ Drug disposition in obese humans: an update. *Clin Pharmacokinet* 1986; **11**: 199–213

3 Abrams B, Parker J. Overweight and pregnancy complications. *Int J Obes* 1988; **12**: 293–303

4 Agarwal N, Shibutani KJ, SanFilippo JA, Del Guercio LRM. Hemodynamic and respiratory changes in surgery of the morbidly obese. *Surgery* 1982, **92**: 226–34

5 Alauddin A, Meterissian S, Lisbona R, MacLean LD, Forse RA. Assessment of cardiac function in patients who were morbidly obese. *Surgery* 1990; **108**: 809–20

6 Alexander JK. Obesity and the circulation *Modern Concepts Cardiovasc Dis* 1963; **32**: 799–803

7 Alexander JK. Obesity and cardiac performance. *Am J Cardiol* 1964; **14**: 860–5

8 Alexander JK, Peterson KL. Cardiovascular effects of weight reduction. *Circulation* 1972, **45**: 310–8

9 Alexander JK, Dennis EW, Smith WG, *et al.* Blood volume, cardiac output, and distribution of systemic blood flow in extreme obesity. *Cardiovasc Res Center Bull* 1962; **1**; 39–44

10 Alpert MA, Hashimi MW. Obesity and the heart. *Am J Med Sci* 1993: **306**: 117–23

11 Alpert MA, Singh A, Terry BE. Effect of exercise on left ventricular function and reserve in morbid obesity. *Am J Cardiol* 1989; **63**: 1478–82

12 Alpert MA, Terry BE, Lambert CR, *et al.* Factors influencing left ventricular systolic function in nonhypertensive morbidly obese patients, and effect of weight loss induced by gastroplasty. *Am J Cardiol* 1993; **71**: 733–7

13 Alpert MA, Lambert CR, Terry BE, *et al.* Influence of left ventricular mass on left ventricular diastolic filling in normotensive morbid obesity. *Am Heart J* 1995; **130**: 1068–73

14 Alpert MA, Lambert CR, Panayiotou H, *et al.* Relation of duration of morbid obesity to left ventricular mass, systolic function, and diastolic filling, and effect of weight loss *Am J Cardiol* 1995; **76**. 1194–7

15 Alpert MA, Lambert CR, Terry BE, *et al.* Effect of weight loss on left ventricular diastolic filling in morbid obesity. *Am J Cardiol* 1995; **76**: 1198–201

16 Alpert MA, Lambert CR, Terry BE, *et al.* Interrelationship of left ventricular mass, systolic function and diastolic filling in normotensive morbidly obese patients. *Int J Obes Relat Metab Disord* 1995; **19**: 550–7

17 Amad KH, Brennan JC, Alexander JK. The cardiac pathology of chronic exogenous obesity. *Circulation* 1965; **32**: 740–5

18 Andersen J, Rasmussen JP, Eriksen J. Pulmonary function in obese patients scheduled for jejuno-ileostomy *Acta Anaesthesiol Scand* 1977; **21**: 346–51

19 Anderson JW, Brinkman-Kaplan VL, Lee H, Wood CL. Relationship of weight loss to cardiovascular risk factors in morbidly obese individuals. *J Am Coll Nutr* 1994; **13**: 256–61

20 Ashwell M, Chinn S, Stalley S, Garrow JS. Female fat distribution—a simple classification based on two circumference measurements. *Int J Obes* 1982; **6**: 143–52

21 Auwerx J, Staels B. Leptin. *Lancet* 1998; **351**: 737–42

22 Azevedo A, Ramos E, von Hafe P, Barros H. Upper-body adiposity and risk of myocardial infarction. *J Cardiovasc Risk* 1999; **6**: 321–5

23 Backman L, Freyschuss V, Hallberg D, Melcher A. Cardiovascular function in extreme obesity. *Acta Med Scand* 1973; **193**: 437–46

24 Bardoczky GI, Yernault JC, Houben JJ, d'Hollander AA. Large tidal volume ventilation does not improve oxygenation in morbidly obese patients during anesthesia. *Anesth Analg* 1995; **81**. 385–8

25 Bennett R, Batenhorst R, Graves DA, Foster TS, Griffen WO, Wright BD. Variation in postoperative analgesic requirements in the morbidly obese following gastric bypass surgery. *Pharmacotherapy* 1982; **2**: 50–3

26 Benotti PN, Bistrain B, Benotti JR, Blackburn G, Forse RA. Heart disease and hypertension in severe obesity: the benefits of weight reduction. *Am J Clin Nutr* 1992; **55**: 586–90

27 Bentley JB, Vaughan RW, Miller MS, Calkins JM, Gandolfi AJ. Serum inorganic fluoride levels in obese patients during and after enflurane anesthesia. *Anesth Analg* 1979; **58**: 409–12

28 Bentley JB, Vaughan RW, Gandolfi AJ, Cork RC Halothane biotransformation in obese and non-obese patients. *Anesthesiology* 1982; **57**: 94–7

29 Berkalp B, Cesur V, Corapcioglu D, Erol C, Baskal N. Obesity and left ventricular diastolic function. *Int J Cardiol* 1995, **52**: 23–6

30 Bharati S, Lev M. Cardiac conduction system involvement in

sudden death of obese young people. *Am Heart J* 1995; **129**: 273–81

31 Bilotta JJ, Floyd JL, Waye JD. Arterial oxygen desaturation during ambulatory colonoscopy: predictability, incidence and clinical insignificance. *Gastrointest Endosc* 1990; **36**: S5–8

32 Biring MS, Lewis MI, Liu JI, Mohsenifar Z. Pulmonary physiologic changes of morbid obesity. *Am J Med Sci* 1999; **318**: 293–7

33 Bjerkedal T. Overweight and hypertension. *Acta Med Scand* 1957; **159**: 13–26

34 Bjorntop P. Visceral obesity: a "civilization syndrome" *Obes Res* 1993; **1**: 206–22

35 Björntorp P. Obesity *Lancet* 1997; **350**: 423–6

36 Blouin RA, Kolpek JH, Mann HJ. Influence of obesity on drug disposition. *Clin Pharm* 1987; **6**: 706–14

37 Boulanger BR, Milzman D, Mitchell K, Rodriguez A. Body habitus as a predictor of injury pattern after blunt trauma. *J Trauma Inj Inf Crit Care* 1992, **33**. 228–32

38 Boulanger BR, Milzman DP, Rodriquez A. Obesity *Crit Care Clin* 1994; **10**: 613–22

39 Bray GA. Pathophysiology of obesity. *Am J Clin Nutr* 1992; **55**: 488S–494S

40 Brodksy JB Anesthetic management of the morbidly obese patient. *Int Anesthesiol Clin* 1986, **24**: 93–103

41 Brodsky JB, Merrel RC. Epidural administration of morphine postoperatively for morbid obese patients *W J Med* 1984; **140**: 750–3

42 Buckley FP. Anesthetizing the morbidly obese patient *ASA Refresher Courses* 1989; **243**: 1–6

43 Buckley FP Anesthesia and obesity and gastrointestinal disorders. In. Barash PG, Cullen BF, Stoelting RK, eds *Clincal Anesthesia*. Philadelphia: J. B. Lippincott, 1992: 1169–83

44 Buckley FP, Robinson NB, Simonowitz DA, Dellinger EP. Anaesthesia in the morbidly obese. A comparison of anaesthetic and analgesic regimens for upper abdominal surgery. *Anaesthesia* 1983; **38**: 840–51

45 Burge JC, Goon A, Choban PS, Flarebaum L Efficacy of hypocaloric total parenteral nutrition in hospitalized obese patients: a prospective, double-blind randomized trial. *J Parenteral Enteral Nutr* 1994; **18**: 203–7

46 Burns SM, Egloff MB, Ryan B, Carpenter R, Burns JE. Effect of body position on spontaneous respiratory effort and tidal volume in patients with obesity, abdominal distension and ascites. *Am J Crit Care* 1994; **3**: 102–6

47 Burwell CS, Robin ED, Whaley RD, Bickelman AG. External obesity associated with alveolar hypoventilation—a Pickwickian syndrome. *Am J Med* 1956; **25**: 815–20

48 Carlsson B, Lindell K, Gabrielsson B, *et al.* Obese (*ob*) gene defects are rare in human obesity. *Obes Res* 1997; **5**. 30–5

49 Cheymol G. Clinical pharmacokinetics of drugs in obesity: an update *Clin Pharmacokinet* 1993, **25**: 103–14

50 Clayton JK, Anderson JR, NcNicol GP. Preoperative prediction of postoperative deep vein thrombosis. *Br Med J* 1976; **ii**: 910–12

51 Connolly LA. Anesthetic management of obstructive sleep apnea patients *J Clin Anesth* 1991; **3**· 461–9

52 Cooper JR, Brodsky JB. Anesthetic management of the morbidly obese patient. *Semin Anesth* 1987; **6**: 260–70

53 Cork RC, Vaughan RW, Bentley JB. General anesthesia for morbidly obese patients—an examination of postoperative outcomes. *Anesthesiology* 1981; **54**: 310–3

54 Damia G, Mascheroni D, Croci M, Tarenzi L Perioperative changes in functional residual capacity in morbidly obese patients. *Br J Anaesth* 1988; **60**: 574–8

55 Daniels SR, Morrison JA, Sprecher DL, Khoury P, Kimball TR. Association of body fat distribution and cardiovascular risk factors in children and adolescents. *Circulation* 1999, **99**. 541–5

56 Dearlove OR, Dobson A, Super M. Anaesthesia and the Präder–Willi syndrome. *Paediatr Anaesth* 1998; **8**: 267–71

57 DeDivitiis O, Fazio S, Petitto M, Maddalena G, Contaldo F, Mancini M. Obesity and cardiac function. *Circulation* 1981, **64**: 477–82

58 De Simone G, Devereux RB, Mureddu GF, *et al.* Influence of obesity on left ventricular midwall mechanics in arterial hypertension. *Hypertension* 1996; **28**: 276–83

59 De Witt Hamer PC, Tuinebreijer WE Preoperative weight gain in bariatric surgery. *Obes Surg* 1998; **8**. 300–1

60 Dominguez-Cherit G, Gonzalez R, Borunda A, Pedroza J, Gonzalez-Barrario J, Herrera MF Anesthesia for morbidly obese patients. *World J Surg* 1998; **22**· 969–73

61 Douglas N, Polo O. Pathogenesis of obstructive sleep apnoea/hypopnoea syndrome. *Lancet* 1994; **344**: 653–5

62 Drenick EJ, Fisler JS. Sudden cardiac arrest in morbidly obese surgical patients unexplained after autopsy *Am J Surg* 1988, **155** 720–6

63 Duflou J, Virmani R, Rabin I, Burke A, Farb A, Smialek J Sudden death as a result of heart disease in morbid obesity. *Am Heart J* 1995, **130**: 306–13

64 Dumont L, Mattys M, Mardirosoff C, Vervloesem N, Alle JL, Massaut J. Changes on pulmonary mechanics during laparoscopic gastroplasty in morbidly obese patients. *Acta Anaesthesiol Scand* 1997; **41**: 408–13

65 Ellis KJ, Abrams SA, Wong WW. Monitoring childhood obesity assessment of the weight/height index *Am J Epidemiol* 1999; **150**. 939–46

66 Eriksson S, Backman L, Ljungstrom KG. The incidence of clinical postoperative thrombosis after gastric surgery for obesity during 16 years. *Obes Surg* 1997, **7**: 332–5

67 Fasol R, Schindler M, Schumacher B, *et al.* The influence of obesity on perioperative morbidity: retrospective study of 502 aortocoronary bypass operations. *Thorac Cardiovasc Surg* 1992; **40**: 126–9

68 Ferraro S, Perrone-Filardi P, Desiderio A, *et al* Left ventricular systolic and diastolic function in severe obesity: a radionuclide study. *Cardiology* 1996; **87**: 347–53

69 Fisher A, Waterhouse TD, Adams AP. Obesity: its relation to anaesthesia. *Anaesthesia* 1975; **30**: 633–47

70 Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL Overweight and obesity in the United States· prevalence and trends, 1960–1994 *Int J Obes Relat Metab Disord* 1998; **22**. 39–47

71 Foley EF, Benotti PN, Borlase BC, Hollingshead J, Blackburn GL Impact of gastric restrictive surgery on hypertension in the morbidly obese. *Am J Surg* 1992; **163**: 294–7

72 Fox GS, Whalley DG, Bevan DR. Anaesthesia for the morbidly obese. *Br J Anaesth* 1981; **53**: 811–6

73 Freedman DS, Dietz WH, Srinivasan SR, Berenson GS The relation of overweight to cardiovascular risk factors among children and adolescents· the Bogalusa Heart Study. *Pediatrics* 1999; **103**: 1175–82

74 Frink EJ, Malan TP, Brown EA, Morgan S, Brown BR Plasma inorganic fluoride levels with sevoflurane anesthesia in morbidly obese and nonobese patients *Anesth Analg* 1993; **76**: 1333–7

75 Garfinkel L. Overweight and cancer. *Ann Int Med* 1985; **103**: 1034–6

76 Garrison RJ, Castelli WP. Weight and thirty-year mortality of men in the Framingham study *Ann Int Med* 1985; **103**: 1006–9

77 Gelman S, Laws HL, Potzick J, Strong S, Smith L, Erdemir H Thoracic epidural vs. balanced anesthesia in morbid obesity: an intraoperative and postoperative hemodynamic study. *Anesth Analg* 1980; **59**: 902–8

78 Gilbert TB, Seneff MG, Becker RB. Facilitation of internal jugular venous cannulation using an audio-guided Doppler ultrasound vascular access device: results from a prospective dual-center, randomized, crossover clinical study. *Crit Care Med* 1995; **23**: 60–5

79 Gratz I, Afshar M, Kidwell P, Weiman DS, Shariff HM. Doppler-guided cannulation of the internal jugular vein: a prospective randomized trial. *J Clin Monitor* 1994; **10**: 185–8

80 Gunnell DJ, Frankel SJ, Nanchahal K, Peters TJ, Davey Smith G. Childhood obesity and adult cardiovascular mortality: a 57-y follow-up study based on the Boyd Orr cohort. *Am J Clin Nutr* 1998; **67**: 1111–8

81 Halaka K, Mustajoki P, Aittomaki J, Sovijarvi AR. Effect of weight loss and body position on pulmonary function and gas exchange abnormalities in morbid obesity. *Int J Obes Relat Metab Disord* 1995; **19**: 343–6, 686

82 Harris T, Cook F, Garrison R, Higgins M, Kannel W, Goldman L. Body mass index and mortality among non-smoking older persons. the Framingham Heart Study. *J Am Med Assoc* 1988; **259**: 1520–4

83 Hedenstierna G. Gas exchange during anaesthesia. *Br J Anaesth* 1990; **64**: 507–14

84 Hodgkinson R, Husain FJ. Obesity and the cephalad spread of analgesia following epidural administration of bupivacaine for cesarian section. *Anesth Analg* 1980; **59**: 89–92

85 Hogan QH, Prost R, Kulier A, Taylor ML, Liu S, Mark L. Magnetic resonance imaging of cerebrospinal fluid volume and the influence of body habitus and abdominal pressure *Anesthesiology* 1996; **84**: 1341–9

86 Holley HS, Milic-Emili J, Becklake MR, Bates DV. Regional distribution of pulmonary ventilation and perfusion in obesity. *J Clin Invest* 1967; **46**: 475–81

87 Hood DD, Dewan DM. Anesthetic and obstetric outcome in morbidly obese parturients. *Anesthesiology* 1993; **79**: 1210–18

88 Hsieh SD, Yoshinaga H. Abdominal fat distribution and coronary heart disease risk factors in men—waist/height ratio as a simple and useful predictor. *Int J Obes Relat Metab Disord* 1995; **19**: 585–9

89 Hubert HB, Feinleib M, McNamara PM, Castelli WB. Obesity as an independent risk factor for cardiovascular disease: A 26-year follow-up of participants in the Framingham heart study. *Circulation* 1983, **67**: 968–77

90 Hunter JD, Reid C, Noble D. Anaesthetic management of the morbidly obese patient. *Hosp Med* 1998; **59**: 481–3

91 Ireton-Jones C, Francis C. Obesity: nutrition support practice and application to critical care. *Nutr Clin Pract* 1995; **10**: 144–9

92 Javier Nieto F. Childhood weight and growth rate as predictors of adult mortality. *Am J Epidemiol* 1992; **136**: 201–13

93 Jeevanandam M, Young DH, Schiller WR. Obesity and the metabolic response to severe multiple trauma in man *J Clin Invest* 1991; **87**: 262–9

94 Jeevanandam M, Ramias L, Schiller WR. Altered plasma amino acid levels in obese traumatized man. *Metabolism* 1991; **40**: 385–90

95 Jennum P, Sjol A. Epidemiology of snoring and obstructive sleep apnoea in a Danish population age 30–60. *J Sleep Res* 1992; **1**: 240–4

96 Jupiter JB, Ring D, Rosen H The complications and difficulties of management of nonunion in the severely obese. *J Orthopaed Trauma* 1995; **9**: 363–70

97 Juvin P, Marmuse JP, Delerme S, *et al.* Post-operative course after conventional or laparoscopic gastroplasty in morbidly obese patients *Eur J Anaesthesiol* 1999; **16**: 400–3

98 Kaltman AJ, Goldring RM. Role of circulatory congestion in the cardiorespiratory failure of obesity. *Am J Med* 1976; **60**. 645–55

99 Kannel WB, Brand N, Skinner JJ, Dawber TR, McNamara PM. The relation of adiposity to blood pressure and the development of hypertension: The Framingham study. *Ann Int Med* 1867; **67**: 48–59

100 Kannel WB, LeBauer JE, Dawber JR, McNamara PM. Relation of body weight to development of coronary heart disease: the Framingham study. *Circulation* 1967; **35**: 734–44

101 Kessler R, Chaouat A, Weitzenblum E, *et al.* Pulmonary hypertension in the obstructive sleep apnea syndrome: prevalence, cause and therapeutic consequences. *Eur Respir J* 1996; **9**: 787–94

102 Kimoff RJ, Cheongt H, Olha AE, *et al.* Mechanisms of apnea termination in obstructive sleep apnea. Role of chemoreceptor and mechanoreceptor stimuli *Am J Respir Crit Care Med* 1994; **149**: 707–14

103 Knaus WA, Draper EA, Wagner DP, Zimmerman JE APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818–28

104 Knaus WA, Wagner DP, Draper EA, *et al* The APACHE III prognostic system: risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; **100**: 1619–36

105 Kochar MS. Hypertension in obese patients. *Postgrad Med* 1993; **93**: 193–200

106 Kral G. Morbid obesity and related health risks (a review). *Ann Int Med* 1985; **103**: 1043–7

107 Kushner RF. Body weight and mortality. *Nutr Rev* 1993; **51**: 127–36

108 Ladergaard-Pederson MJ. Recovery from general anesthesia in obese patients. *Anesthesiology* 1981; **55**: 720

109 Laks L, Krieger J, Podszus T. Pulmonary hypertension in obstructive sleep apnea: multicenter study. *Am Rev Respir Dis* 1992; **145**: 865

110 Lam AM, Grace DM, Penny F, Vezina WC Prophylactic intravenous cimetidine reduces the risk of acid aspiration in morbidly obese patients. *Anesthesiology* 1983; **59**: A242

111 Lean ME. Obesity and cardiovascular disease: the waisted years. *Br J Cardiol* 1999; **6**: 269–73

112 Lee JJ, Larson RH, Buckley JJ, Roberts RB. Airway maintenance in the morbidly obese. *Anesth Rev* 1980; **7**: 33–6

113 Luce JM. Respiratory complications of obesity. *Chest* 1980; **78**: 626–31

114 Makk LJK, McClave DSA, Creech PW. Clinical application of the metabolic cart to the delivery of total parenteral nutrition. *Crit Care Med* 1990; **18**: 1320–7

115 Marik P, Varon J. The obese patient in the ICU. *Chest* 1998; **113**: 492–8

116 Manson JE. Colditz GA, Stampfer MJ, *et al.* A prospective study of obesity and risk of coronary heart disease in women. *New Engl J Med* 1990; **322**: 882–9

117 Mayersohn M, Calkins JM, Perrier DG, *et al.* Thiopental kinetics in obese patients. *Anesthesiology* 1981; **55**: 178A

118 Messerli FH, Sundgaard-Riise K, Reisen E, Dreslinski GR, Dunn FG, Frohlich E. Disparate cardiovascular effects of obesity and arterial hypertension. *Am J Med* 1983; **74**: 808–12

119 Mikhail N, Golub MS, Tuck ML. Obesity and hypertension. *Prog Cardiovasc Dis* 1999; **42**: 39–58

120 Millman RP, Meyer TJ, Eveloff SE. Sleep apnea in the morbidly obese. *Rhode Island Med* 1992; **75**: 483–6

121 Murphy PG. Obesity. In: Hemmings HC Jr, Hopkins PM, eds

Foundations of Anaesthesia Basic and Clinical Sciences. London: Mosby, 2000; 703–11

122 National Institutes of Health Consensus Development Conference Statement Health implications of obesity. *Ann Int Med* 1985; **103**· 147–51

123 Øberg B, Poulsen TD. Obesity: an anaesthetic challenge *Acta Anaesthesiol Scand* 1996; **40**: 191–200

124 Partinen M, Guilleminault C. Daytime sleepiness and vascular morbidity at seven-year follow-up in obstructive sleep apnea patients. *Chest* 1990; **97**: 27–32

125 Pasulka PS, Bistrian BR, Benotti PN The risks of surgery in obese patients. *Ann Int Med* 1986; **104**: 540–6

126 Paul DR, Hoyt JL, Boutros AR. Cardiovascular and respiratory changes in response to change of posture in the very obese. *Anesthesiology* 1976; **45** 73–8

127 Pelosi P, Ravagnan I, Giurati G, Panigada M, Buttoni N, Tredici S Positive end-expiratory pressure improves respiratory function in obese but not in normal subjects during anesthesia and paralysis. *Anesthesiology* 1999; **91** 1221–31

128 Pelosi P, Croci M, Ravagnan I, Vicardi P, Gattinoni L Total respiratory system, lung, and chest wall mechanics in sedated–paralyzed postoperative morbidly obese patients *Chest* 1996; **109**: 144–51

129 Pelosi P, Croci M, Ravgnan I, *et al.* The effect of body mass on lung volumes, respiratory mechanics, and gas exchange during general anesthesia. *Anesth Analg* 1998; **87**: 645–60

130 Perlow JH, Morgan MA. Massive maternal obesity and perioperative cesarean morbidity. *Am J Obstet Gynecol* 1994; **70**· 560–5

131 Perry AC, Applegate EB, Allison MD, Jackson ML, Miller PC Clinical predictability of the waist-to-hip ratio in assessment of cardiovascular disease risk factors in overweight, pre-menopausal women. *Am J Clin Nutr* 1998; **68**: 1022–7

132 Pitkanen MT. Body mass and spread of spinal anesthesia with bupivacaine *Anesth Analg* 1987; **66**: 127–31

133 Raucoles-Aime M, Brimaud D. Diabetes mellitus. Implications for the anesthesiologist. *Curr Opin Anesth* 1996; **9**: 247–51

134 Rawal N, Sjostrand U, Christofferson E, Dahlstrom B, Arvill A, Rydman H. Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese. Influence on postoperative ambulation and pulmonary function. *Anesth Analg* 1984; **63**: 583–92

135 Ray C, Sue D, Bray G, Hansen JE, Wasserman K. Effects of obesity on respiratory function. *Am Rev Respir Dis* 1983; **128**: 501–6

136 Reeder BA, Senthilselvan A, Despres JP, *et al.* The association of cardiovascular disease risk factors with abdominal obesity in Canada. Canadian Heart Health Surveys Research Group *Can Med Assoc J* 1997, **157**: S39–45

137 Rose DK, Cohen MM, Wigglesworth DF, De Boer F. Critical respiratory events in the postanesthesia care unit: patient, surgical and anesthetic factors. *Anesthesiology* 1994; **81**: 410–18

138 Salem MR, Dalal FY, Zygmunt MP, Mathrubhutham M, Jacobs HK Does PEEP improve intraoperative arterial oxygenation in grossly obese patients? *Anesthesiology* 1978; **48**: 280–1

139 Santesson J. Oxygen transport and venous admixture in the extremely obese. Influence of anaesthesia and artificial ventilation with and without positive end-expiratory pressure. *Acta Anaesthesiol Scand* 1977; **21**: 56–61

140 Saunders R. Binge eating in gastric bypass patients before surgery. *Obes Surgery* 1999, **9**. 72–6

141 Schafer H, Ewig S, Hasper E, Luderitz B. Failure of CPAP therapy in obstructive sleep apnoea syndrome: predictive factors and treatment with bilevel-positive airway pressure. *Resp Med* 1998; **92**: 208–15

142 Shenkman Z, Shir Y, Brodsky JB. Perioperative management of the obese patient. *Br J Anaesth* 1993, **70** 349–59

143 Sjostrom LV. Mortality of severely obese subjects. *Am J Clin Nutr* 1992; **55**. 516S–23S

144 Smith HL, Willius FA Adiposity of the heart. *Arch Int Med* 1973, **52**: 929–31

145 Smith-Choban P, Weireter LJ, Maynes C. Obesity and increased mortality in blunt trauma *J Trauma* 1991; **31**. 1253–7

146 Snider RD, Kruse JA, Bander JJ, Dunn GH. Accuracy of estimated creatinine clearance in obese patients with stable renal function in the intensive care unit *Pharmacotherapy* 1995; **15**· 747–53

147 Sobal J, Stunkard A. Socioeconomic status of obesity· a review of the literature. *Psychol Bull* 1989; **105**. 260–75

148 Soderberg M, Thomson D, White T. Respiration, circulation and anaesthetic management in obesity. Investigation before and after jejunoileal bypass. *Acta Anaesthesiol Scand* 1977; **21**: 55–61

149 Strube PJ, Hulands GH, Halsey MJ Serum fluoride levels in morbidly obese patients: Enflurane compared with isoflurane anaesthesia. *Anaesthesia* 1987, **42**: 685–9

150 Stunkard AJ. Current views on obesity. *Am J Med* 1996, **100**: 230–5

151 Taivainen T, Tuominen M, Rosenberg PM. Influence of obesity on the spread of spinal analgesia after injection of plain 0.5% bupivacaine at the L_{3-4} or L_{4-5} interspace. *Br J Anaesth* 1990, **64**: 542–6

152 Tosetti C, Corinaldesi R, Stanghellini V, *et al.* Gastric emptying of solids in morbid obesity *Int J Obes Relat Metab Disord* 1996; **20**. 200–5

153 Tsueda K, Debrand M, Zeok SS, Wright BD, Griffin WO. Obesity supine death syndrome. reports of two morbidly obese patients. *Anesth Analg* 1979; **58**: 345–7

154 Valensi P, Thi BN, Lormeau B, Paries J, Attali JR Cardiac autonomic function in obese patients. *Int J Obes Relat Metab Disord* 1995; **19**· 113–18

155 VanDercar DH, Martinez AP, De Lisser EA. Sleep apnea syndromes: a potential contraindication for patient-controlled analgesia. *Anesthesiology* 1991; **74**: 623–4

156 Vaughan RW. Anesthetic management of the morbidly obese patient. In. Brown BR, Blitt CD, Giesecke AH, Vaughan RW, eds. *Anesthesia and the Obese Patient* New York. Davis, 1982, 71–94

157 Vaughan RW, Wise L Postoperative arterial blood gas measurement in obese patients. effects of position on gas exchange. *Ann Surg* 1975; **182**: 705–9

158 Vaughan RW, Wise L Intraoperative arterial oxygenation in obese patients. *Ann Surg* 1976; **184**: 35–42

159 Vaughan RW, Bauer S, Wise L Volume and pH of gastric juice in obese patients. *Anesthesiology* 1975; **43**: 686–9

160 Vaughan RW, Bauer S, Wise L Effect of position (semirecumbent versus supine) on postoperative oxygenation in markedly obese subjects. *Anesth Analg* 1976; **55**: 37–41

161 Vgontzas AN, Tan TL, Bixler EO, *et al.* Sleep apnea and sleep disruption in obese patients. *Arch Int Med* 1994, **154**. 1705–11

162 Vila P, Valles J, Canet J, Melero A, Vidal F. Acid aspiration prophylaxis in morbidly obese patients: famotidine vs ranitidine. *Anaesthesia* 1991; **46**. 967–9

163 Wallace DH, Currie JM, Gilstrap LC, Santos R Indirect sonographic guidance for epidural anesthesia in obese pregnant patients. *Reg Anesth* 1992; **17**: 233–6

164 Waltemath CL, Bergman NA. Respiratory compliance in obese patients. *Anesthesiology* 1974; **41**: 84–5

165 Warnes CA, Roberts WC. The heart in massive (more than 300 pounds or 136 kilograms) obesity: analysis of 12 patients studied at necropsy. *Am J Cardiol* 1984; **54**: 1087–91

166 Wasan KM, Lopex-Berestein G. The influence of serum lipoproteins on the pharmacokinetics and pharmacodynamics of lipophilic drugs and drug carriers. *Arch Med Res* 1993; **24**: 395–401

167 Williamson JA, Webb RK, Szekely S, Gillies ER, Dreosti AV. The Australian Incident Monitoring Study: difficult intubation: an analysis of 2000 incident reports. *Anaesth Intensive Care* 1993; **21**: 602–7

168 Wisen O, Hellstrom PM. Gastrointestinal motility in obesity. *J Int Med* 1995; **273**: 411–18

169 Young T, Palta M, Dempsey J, Skatrud J, Webber S, Bader S. The occurrence of sleep-disordered breathing among middle-aged adults. *New Engl J Med* 1993; **328**: 1230–5

170 Zacchi P, Mearin F, Humbert P, Formiguera X, Malagelada JR. Effect of obesity on gastroesophageal resistance to flow in man. *Dig Dis Sci* 1991; **36**: 1473–80

171 Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse *obese* gene and its human homologue. *Nature* 1994; **372**: 425–32

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The stress response to trauma and surgery

J. P. Desborough

Department of Anaesthesia, Epsom General Hospital, Dorking Road, Epsom KT18 7EG, UK

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The stress response is the name given to the hormonal and metabolic changes which follow injury or trauma. This is part of the systemic reaction to injury which encompasses a wide range of endocrinological, immunological and haematological effects (Table 1). The responses to surgery have been of interest to scientists for many years. In 1932, Cuthbertson described in detail the metabolic responses of four patients with lower limb injuries.[10] He documented and quantified the time course of the changes. The terms 'ebb' and 'flow' were introduced to describe an initial decrease and subsequent increase in metabolic activity. The description of the 'ebb' phase was based partly on work in experimental animals and the estimations of increases in metabolic rate in the 'flow' phase were exaggerated. These descriptions have been perpetuated and are still quoted, but have been redefined[29] and are perhaps not critical to an understanding of the actual changes which occur.

After the early work on the stress response to accidental injury, attention turned to surgical trauma, and responses to most types of surgery were reported. Following on from this, the ability of anaesthetic agents and neural blockade to modify the endocrine and metabolic responses has been studied enthusiastically. Although it seems that the stress response developed to allow injured animals to survive by catabolizing their own stored body fuels, it has been argued that the response is unnecessary in current surgical practice. Strenuous efforts have been made to inhibit the stress responses to surgery and evaluate the outcome. In particular, the potential benefits of regional anaesthesia on surgical outcome are still under scrutiny. Over the past 10 yr, the role of cytokines in the response to surgery, and the interaction between the immunological and neuroendocrine systems, has furthered interest in the subject. This review describes the endocrine and metabolic changes which occur during surgery, and the effects of anaesthetic and analgesic regimens upon the responses.

Table 1 Systemic responses to surgery

Sympathetic nervous system activation
Endocrine 'stress response'
  pituitary hormone secretion
  insulin resistance
Immunological and haematological changes
  cytokine production
  acute phase reaction
  neutrophil leucocytosis
  lymphocyte proliferation

The endocrine response to surgery

The stress response to surgery is characterized by increased secretion of pituitary hormones and activation of the sympathetic nervous system.[13] The changes in pituitary secretion have secondary effects on hormone secretion from target organs (Table 2). For example, release of corticotrophin from the pituitary stimulates cortisol secretion from the adrenal cortex. Arginine vasopressin is secreted from the posterior pituitary and has effects on the kidney. In the pancreas, glucagon is released and insulin secretion may be diminished. The overall metabolic effect of the hormonal changes is increased catabolism which mobilizes substrates to provide energy sources, and a mechanism to retain salt and water and maintain fluid volume and cardiovascular homeostasis.

Table 2 Principal hormonal responses to surgery. ACTH, adrenocorticotrophic hormone (corticotrophin), AVP, arginine vasopressin, FSH, follicle-stimulating hormone; LH, luteinizing hormone, TSH, thyroid-stimulating hormone Based on Desborough and Hall[13]

Endocrine gland	Hormones	Change in secretion
Anterior pituitary	ACTH	Increases
	Growth hormone	Increases
	TSH	May increase or decrease
	FSH and LH	May increase or decrease
Posterior pituitary	AVP	Increases
Adrenal cortex	Cortisol	Increases
	Aldosterone	Increases
Pancreas	Insulin	Often decreases
	Glucagon	Usually small increases
Thyroid	Thyroxine, tri-iodothyronine	Decrease

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Sympathoadrenal response

Hypothalamic activation of the sympathetic autonomic nervous system results in increased secretion of catecholamines from the adrenal medulla and release of norepinephrine from presynaptic nerve terminals. Norepinephrine is primarily a neurotransmitter, but there is some spillover of norepinephrine released from nerve terminals into the circulation. The increased sympathetic activity results in the well recognized cardiovascular effects of tachycardia and hypertension. In addition, the function of certain visceral organs, including the liver, pancreas and kidney, is modified directly by efferent sympathetic stimulation and/or circulating catecholamines.

The hypothalamic–pituitary–adrenal axis

Anterior pituitary

Anterior pituitary hormone secretion is stimulated by hypothalamic releasing factors.[32] The pituitary synthesizes corticotrophin or adrenocorticotrophic hormone (ACTH) as part of a larger precursor molecule, pro-opiomelanocortin. The precursor is metabolized within the pituitary into ACTH, β-endorphin and an N-terminal precursor. Growth hormone and prolactin are also secreted in increased amounts from the pituitary in response to a surgical stimulus. Concentrations of the other anterior pituitary hormones, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) do not change markedly during surgery.

Posterior pituitary

The posterior pituitary produces arginine vasopressin which has a major role as an antidiuretic hormone. It also has an endocrine function, acting with corticotrophin-releasing factor in stimulating the secretion of pro-opiomelanocortin from the anterior pituitary.

Corticotrophin

Corticotrophin (ACTH) is a 39 amino acid peptide, produced in the pituitary from the larger molecule, pro-opiomelanocortin. ACTH stimulates the adrenal cortical secretion of glucocorticoids so that circulating concentrations of cortisol are increased. Surgery is one of the most potent activators of ACTH and cortisol secretion, and increased plasma concentrations of both hormones can be measured within minutes of the start of surgery.

Growth hormone

Growth hormone is a protein of 191 amino acids secreted from the anterior pituitary.[13] Its release is stimulated by growth hormone releasing factor from the hypothalamus. Growth hormone, also known as somatotrophin, has a major role in growth regulation, particularly in the perinatal period and in childhood. Many of its actions are mediated through small protein hormones called insulin-like growth factors (IGFs), notably IGF-1, which is produced in liver, muscle and other tissues in response to stimulation by growth hormone. In addition to the regulation of growth, growth hormone has many effects on metabolism. It stimulates protein synthesis and inhibits protein breakdown, promotes lipolysis (the breakdown of triglycerides into fatty acids and glycerol) and has an anti-insulin effect. This means that growth hormone inhibits glucose uptake and use by cells, which spares glucose for use by neurones in situations of glucose scarcity. Growth hormone may also stimulate glycogenolysis in the liver. Growth hormone secretion from the pituitary increases in response to surgery and trauma, in relation to the severity of the injury.

β-Endorphin and prolactin

β-Endorphin is an opioid peptide of 31 amino acids produced from the precursor molecule proopiomelanocortin. Increased β-endorphin concentrations in the circulation after surgery reflect increased pituitary hormone secretion. The hormone has no major metabolic activity.

Prolactin is a protein hormone of 199 amino acids with a structure similar to that of growth hormone. Secretion of prolactin is increased as part of the stress reponse to surgery and also during exercise. It has little metabolic activity. Prolactin production increases during pregnancy and stimulates milk secretion from the breast.

Cortisol

Cortisol secretion from the adrenal cortex increases rapidly following the start of surgery, as a result of stimulation by ACTH. From baseline values of around 400 nmol litre^{-1}, cortisol concentrations increase to a maximum at about 4–6 h, and may reach >1500 nmol litre^{-1} depending on the severity of the surgical trauma.[38] The cortisol response can be modified by anaesthetic intervention (see below).

Usually, a feedback mechanism operates so that increased concentrations of circulating cortisol inhibit further secretion of ACTH. This control mechanism appears to be ineffective after surgery so that concentrations of both hormones remain high.

Cortisol has complex metabolic effects on carbohydrate, fat and protein. It promotes protein breakdown and gluconeogenesis in the liver. Glucose use by cells is inhibited, so that blood glucose concentrations are increased. Cortisol promotes lipolysis, which increases the production of gluconeogenic precursors from the breakdown of triglyceride into glycerol and fatty acids.

Cortisol has other glucocorticoid effects, notably those associated with anti-inflammatory activity. Corticosteroids inhibit the accumulation of macrophages and neutrophils into areas of inflammation and can interfere with the synthesis of inflammatory mediators, particularly prostaglandins.

Insulin and glucagon

Insulin is the key anabolic hormone.[13] It is a polypeptide with two chains (of 21 and 30 amino acids) linked by two disulphide bridges. Insulin is synthesized and secreted by the β cells of the pancreas. It is released after food intake, when blood glucose and amino acid concentrations increase. Insulin promotes the uptake of glucose into muscle and adipose tissue and the conversion of glucose into glycogen and triglycerides. It also stimulates the formation of glycogen from glucose in the liver Protein catabolism and lipolysis are inhibited by insulin.

Insulin concentrations may decrease after the induction of anaesthesia, and during surgery there is a failure of insulin secretion to match the catabolic, hyperglycaemic response. This may be caused partly by α-adrenergic inhibition of β cell secretion. In addition, there is a failure of the usual cellular response to insulin, the so-called 'insulin resistance', which occurs in the perioperative period.

Glucagon is produced in the α cells of the pancreas. This hormone promotes hepatic glycogenolysis. It also increases gluconeogenesis from amino acids in the liver and has lipolytic activity. Although plasma glucagon concentrations increase transiently after major surgery, this does not make a major contribution to the hyperglycaemic response.

Thyroid hormones

Thyroxine (T_4) and tri-iodothyronine (T_3) are secreted into the circulation from the thyroid gland under the influence of thyroid-stimulating hormone (TSH). Small amounts of inactive, reverse T_3 (rT_3) are produced from the thyroid. T_3 is formed in the tissues by the monodeiodination of T_4. T_3 is three to five times more active metabolically than T_4. The hormones are bound extensively to their binding proteins, albumin, thyroxine-binding pre-albumin and thyroid-binding globulin (TBG). The free thyroid hormones in the plasma are metabolically active. Very low concentrations of free T_3 and T_4 are present in the circulation and are in equilibrium with bound hormone in the plasma and the tissues.[15]

Thyroid hormones stimulate the oxygen consumption of most of the metabolically active tissues of the body. Notable exceptions are the brain, spleen and the anterior part of the pituitary gland. As a result of thyroid hormone activity, metabolic rate and heat production is increased. The other principal actions of thyroid hormones are to increase carbohydrate absorption from the gut, to stimulate both the central and peripheral nervous systems and, in the longer term, to influence growth and development.

There is a close association between the activity of thyroid hormones and the catecholamines. In general terms, epinephrine and norepinephrine increase the metabolic rate and stimulate the nervous system. The thyroid hormones increase the number and affininty of β-adrenoceptors in the heart and, ultimately, increase the sensitivity of the heart to the actions of catecholamines.

Concentrations of total and free T_3 decrease after surgery and return to normal after several days. TSH concentrations decrease during the first 2 h and then return to preoperative levels. The reason for the changes remains unclear, but may be influenced by the close relationship between thyroid hormones, catecholamines and cortisol. Exogenous steroids suppress T_3, so hypercortisolaemia after surgery may also depress T_3 concentrations.[11]

Gonadotrophins

The gondotrophins, LH and FSH, are secreted from the anterior pituitary. FSH is responsible for the development of ovarian follicles in females. In males, FSH maintains the spermatic epithelium.

LH stimulates growth and development of the Leydig cells of the testis which produce testosterone. In females, LH promotes maturation of the ovarian follicles and the secretion of oestrogen. It also stimulates the formation of the corpus luteum from the follicles after ovulation.

Testosterone is a steroid manufactured from cholesterol in the Leydig cells of the testis It has a negative feedback effect on LH secretion from the anterior pituitary. It has important effects on protein anabolism and on growth, in addition to its well known role in the development and maintainance of male secondary sexual characteristics.

The significance of changes in pituitary gonadotrophins following surgery requires further study. Testosterone concentrations are decreased for several days, while LH concentrations show variable changes.[51] In female subjects, oestradiol concentrations decrease for up to 5 days postoperatively.[50]

Metabolic sequelae of the endocrine response

The net effect of the endocrine response to surgery is an increased secretion of catabolic hormones. This promotes the provision of food substrates from the catabolism of carbohydrate, fat and protein. In evolutionary terms, it seems likely that the stress response developed as a survival mechanism which allowed injured animals to sustain themselves until their injuries were healed. By using stored body fuels and retaining salt and water, the animal had a chance to survive without food until healing and repair had taken place. In current surgical and anaesthetic practice, it is questionable whether the stress response is necessary.

Carbohydrate metabolism

Blood glucose concentrations increase after surgery begins Cortisol and catecholamines facilitate glucose production as a result of increased hepatic glycogenolysis and gluconeogenesis. In addition, peripheral use of glucose is decreased

Blood glucose concentrations are related to the intensity of the surgical injury; the changes follow closely the increases in catecholamines. In cardiac surgery, blood glucose concentrations can increase up to 10–12 mmol litre^{-1} and remain elevated for >24 h after surgery. The changes are less marked with minor surgery.

The usual mechanisms that maintain glucose homeostasis are ineffective in the perioperative period. Hyperglycaemia persists because catabolic hormones promote glucose production and there is a relative lack of insulin together with peripheral insulin resistance.

In diabetic subjects it is now established that poor glycaemic control is associated with an increase in diabetic complications, which can be avoided with tight control of blood glucose[47] (see paper by Halls). The risks of prolonged perioperative hyperglycaemia are less well established, although potential risks include wound infection and impaired wound healing. An increased incidence of wound infection and mediastinitis was found in diabetics and non-diabetics in whom blood glucose concentrations were >200 mg dl^{-1} after cardiac surgery.[49]

Protein metabolism

Protein catabolism is stimulated by increased cortisol concentrations. Predominantly skeletal muscle is broken down, but some visceral muscle protein is also catabolized to release the constituent amino acids. The amino acids may be further catabolized for energy or used in the liver to form new protein, particularly acute-phase proteins. The liver also converts amino acids into other substrates, glucose, fatty acids or ketone bodies. Protein catabolism results in marked weight loss and muscle wasting in patients after major surgical and traumatic injury. The loss of protein can be measured indirectly by increased nitrogen excretion in the urine.

There has been much interest in the provision of nutritional supplements for patients with critical illness and those undergoing major surgery. Certain nutrients may have a beneficial influence on the immune status of stressed patients. Glutamine, arginine, glycine, ω-3 polyunsaturated fatty acids and nucleotides have been studied most extensively.[44] Glutamine and arginine are semi-essential amino acids with multiplicity of functions including stimulation of immune activity. Studies of patients given enteral nutrition supplemented with arginine or glycine after major surgery benefited from a faster recovery of immunological parameters, fewer infectious complications and a shorter hospital stay.[44]

Fat metabolism

As a result of hormonal changes during surgery, fats stored as triglycerides are converted by lipolysis to glycerol and fatty acids. Lipolytic activity is stimulated by cortisol, catecholamines and growth hormone and is inhibited in the presence of insulin. The net result is increased mobilization of triglyceride, although plasma concentrations of glycerol and fatty acids may not change markedly. The glycerol produced by lipolysis is a substrate for gluconeogenesis in the liver. Fatty acids enter a 'pool' from which they may be oxidized in the liver and in muscle, converted to ketone bodies or re-esterified.

Water and electrolyte metabolism

A number of hormonal changes occur in response to surgery which influence salt and water metabolism. These changes support the preservation of adequate body fluid volumes. Arginine vasopressin, which is released from the posterior pituitary, promotes water retention and the production of concentrated urine by direct action on the kidney. Increased vasopressin secretion may continue for 3–5 days, depending on the severity of the surgical injury and the development of complications.

Renin is secreted from the juxtaglomerular cells of the kidney, partly as a result of increased sympathetic efferent activation. Renin stimulates the production of angiotensin II. This has a number of important effects; in particular, it stimulates the release of aldosterone from the adrenal cortex, which in turn leads to Na^+ and water reabsorption from the distal tubules in the kidney.[11]

Activation of the stress response

The endocrine response is activated by afferent neuronal impulses from the site of injury. These travel along sensory nerve roots through the dorsal root of the spinal cord, up the spinal cord to the medulla to activate the hypothalamus.

In the 1950s it was postulated that there might be 'wound hormones' produced in injured tissues which activated the pituitary–adrenal axis. In classical experiments, Egdahl demonstrated the role of the nervous system in the activation of the stress response.[16] He studied the adrenocortical responses to limb injury in dogs with innervated and denervated extremities. Blood samples were collected from the adrenal vein for assay of adrenal corticosteroid concentration. In animals with an intact sciatic nerve, operative injury and burns to the limb resulted in an immediate and sustained increase in adrenal hormone concentration in samples from the adrenal vein. If the nerve was cut after the injury, there was a rapid decline in the hormone response. In those animals in which the sciatic nerve was transected before operative or burn injury, there was no increase in adrenal hormone after the trauma. This work did not provide evidence that local substances were released after injury which stimulated the pituitary–adrenal axis. The idea that local substances might influence some of the changes associated with surgery was advanced by the discovery of the cytokines.

Cytokines

Cytokines are a group of low-molecular-weight proteins which include the interleukins and interferons. They are produced from activated leucocytes, fibroblasts and endothelial cells as an early response to tissue injury and have a major role in mediating immunity and inflammation.[42] The cytokines act on surface receptors on many different target cells and their effects are produced ultimately by influencing protein synthesis within these cells. Details of the cytokine network and the activation of cytokines in response to surgery have been reviewed recently.[19 42] The effects of chronic stimulation of the cytokine network, for example, in sepsis, has also been reviewed.[6]

The cytokines have a major role in the inflammatory response to surgery and trauma. They have local effects of mediating and maintaining the inflammatory response to tissue injury, and also initiate some of the systemic changes which occur. After major surgery, the main cytokines released are interleukin-1 (IL-1), tumour necrosis factor-α (TNF-α) and IL-6. The initial reaction is the release of IL-1 and TNF-α from activated macrophages and monocytes in the damaged tissues. This stimulates the production and release of more cytokines, in particular, IL-6, the main cytokine responsible for inducing the systemic changes known as the acute phase response.[42]

Interleukin-6

This is a 26 kDa protein. Concentrations of circulating cytokines are normally low and may be undetectable. Within 30–60 min after the start of surgery, IL-6 concentration increases; the change in concentration becomes significant after 2–4 h. Cytokine production reflects the degree of tissue trauma, so cytokine release is lowest with the least invasive and traumatic procedures, for example, laparoscopic surgery. The largest increases in IL-6 occur after major procedures such as joint replacement, major vascular and colorectal surgery. After these operations, cytokine concentrations are maximal at about 24 h and remain elevated for 48–72 h postoperatively.

The acute phase response

A number of changes occur following tissue injury which are stimulated by cytokines, particularly IL-6. This is known as the 'acute phase response'; one of its features is the production in the liver of acute phase proteins (Table 3). These proteins act as inflammatory mediators, anti-proteinases and scavengers and in tissue repair. They include C-reactive protein (CRP), fibrinogen, α_2-macroglobulin and other anti-proteinases. The increase in serum concentrations of CRP follows the changes in IL-6. Production of other proteins in the liver, for example, albumin and transferrin, decreases during the acute phase response. Concentrations of circulating cations such as zinc and iron decrease, partly as a consequence of the changes in the production of the transport proteins.[42]

Table 3 Features of the acute phase response C, C-reactive protein Based on Sheeran and Hall[42]

- Fever
- Granulocytosis
- Production of acute phase proteins in liver
  - CRP
  - fibrinogen
  - α_2-macroglobulin
- Changes in serum concentrations of transport proteins
  - increase in ceruloplasmin
  - decrease in transferrin, albumin and α_2-macroglobulin
- Changes in serum concentrations of divalent cations
  - copper increases
  - zinc and iron decrease

Interaction between the immune system and the neuroendocrine system

The cytokines IL-1and IL-6 can stimulate secretion of ACTH from isolated pituitary cells *in vitro*. In patients after surgery, cytokines may augment pituitary ACTH secretion and subsequently increase the release of cortisol. A negative feedback system exists, so that glucocorticoids inhibit cytokine production. The cortisol response to surgery is sufficient to depress IL-6 concentrations.[20]

Minimally invasive surgery

Laparoscopic surgery causes less tissue injury than conventional procedures, so the increase in concentrations of biochemical markers of inflammation, such as IL-6 and the acute phase protein, CRP, is not as great.[21] The classical stress responses (catecholamines, cortisol and glucose) to abdominal surgery such as cholecystectomy, are not changed greatly by reducing surgical trauma. This suggests that stimuli for the stress response arise from visceral and peritoneal afferent nerve fibres in addition to those from the abdominal wall. Anaesthesia has little effect on the cytokine response to surgery because it cannot influence tissue trauma. Although regional anaesthesia inhibits the stress response to surgery, it has no significant effect on cytokine production. Combined analgesic regimens which included high-dose steroids showed a small decline in IL-6 concentrations and the acute phase response because of the interaction of glucocorticoids and cytokines.[41] The technique was accompanied by unwanted side-effects, including wound breakdown.

The effect of anaesthesia on the stress response to surgery

General anaesthesia

Opioids

It has been known for many years that opioids suppress hypothalamic and pituitary hormone secretion. McDonald and colleagues demonstrated the suppressant effect of therapeutic doses of morphine on the hypothalamic–pituitary–adrenal axis in humans.[33] Morphine suppressed the release of corticotrophin and, consequently, cortisol in normal and stress conditions, although the adrenals were found to respond to exogenous administration of ACTH. The inhibitory effects of morphine occur at the hypothalamic level.

In cardiac surgery, the effects of morphine and other opioids on the stress response to surgery have been well documented.[12] Large doses of morphine (4 mg kg^{-1}) block the secretion of growth hormone and inhibit cortisol release until the onset of cardiopulmonary bypass (CPB). Fentanyl (50–100 μg kg^{-1}), sufentanil (20 μg kg^{-1}) and alfentanil (1.4 mg kg^{-1}) suppress pituitary hormone secretion until CPB.[12] After the onset of CPB, the physiological changes are so profound that the hypothalamic and pituitary responses cannot be completely inhibited by opioids. A high-dose opioid technique leads inevitably to respiratory depression after surgery, which requires ventilatory support to be provided for the patient in the postoperative period.

In lower abdominal surgery, fentanyl 50 μg kg^{-1} will suppress the growth hormone, cortisol and glycaemic changes found during pelvic surgery.[18] In this study, the opioid was administered during induction of anaesthesia. When fentanyl 50 μg kg^{-1} was given 60 min after the start of pelvic surgery, there was no significant effect on the endocrine response which was already established.[5] It was subsequently established that fentanyl 15 μg kg^{-1} was sufficient to inhibit cortisol and glucose responses to lower abdominal surgery.[26]

In upper abdominal surgery, systemic opioids are relatively ineffective in preventing the stress response to upper abdominal surgery. Fentanyl 100 μg kg^{-1} abolished completely the hormonal changes after conventional cholecystectomy, but the technique resulted in respiratory depression requiring ventilatory support in the postoperative period.[24]

Etomidate and benzodiazepines

The anaesthetic induction agent etomidate is a carboxylated imidazole that interferes with the production of steroids in the adrenal cortex by reversible inhibition of the enzyme 11β-hydroxylase and cholesterol side-chain cleavage enzyme. The synthesis of both aldosterone and cortisol is blocked. A single induction dose of the drug will suppress hormone production for 6–12 h,[48] while infusion for 1–2 h blocks cortisol synthesis for up to 24 h.[37] In healthy patients, there were no adverse cardiovascular effects from such an infusion during pelvic surgery, and the only metabolic result of cortisol inhibition was a decrease in the expected glycaemic response.[25]

The use of etomidate by infusion as part of intravenous sedation for critically ill patients was found to be associated with increased mortality.[27] As a result, the drug is no longer licensed for use in long-term sedation. A recent study has examined adrenocortical function in critically ill patients after induction of anaesthesia with etomidate or thiopental.[3] Pre-induction cortisol concentrations were measured and a short ACTH stimulation test was performed at 24 h to assess adrenal function. Cortisol concentrations before induction of anaesthesia were high, in keeping with other studies of adrenal function in critically ill patients. Those patients who received etomidate tended to have a smaller cortisol response to stimulation by ACTH than the control thiopental group. Although assessment of adrenocortical function in critically ill patients using single cortisol concentrations and ACTH stimulation tests is the subject of great controversy,[34] this study suggests that etomidate may interfere with cortisol synthesis in these patients.[3]

The benzodiazepine, midazolam, which has an imidazole ring in addition to the basic benzodiazepine structure, attenuates the cortisol responses to both peripheral and upper abdominal surgery.[9 14] Midazolam and diazepam both inhibit cortisol production from isolated bovine adrenocortical cells *in vitro*. Although Crozier and colleagues showed that subjects produced cortisol in response to exogenous ACTH,[9] thus confirming that the site of action of the benzodiazepine is at the hypothalamic–pituitary level, a direct inhibitory effect on steroid production cannot be excluded.

Clonidine

Clonidine is a centrally acting antihypertensive drug which activates α_2-adrenergic receptors.[1] It provides haemodynamic stability through its sympatholytic activity, and can reduce anaesthetic and analgesic requirements and provide sedation. By reducing the sympathoadrenal and cardiovascular responses caused by noxious surgical stimuli, the α_2-agonists inhibit the stress responses mediated by the sympathetic nervous system.

Regional anaesthesia

Extensive epidural analgesia with local anaesthetic agents will prevent the endocrine and metabolic responses to surgery in the pelvis and on the lower limbs. Epidural blockade from dermatomal segment T4 to S5, established before the start of surgery, prevented increases in cortisol and glucose concentrations in response to hysterectomy.[17] Both afferent input from the operative site to the central nervous system and the hypothalamic–pituitary axis, and efferent autonomic neuronal pathways to the liver and adrenal medulla are blocked. Thus the adrenocortical and glycaemic responses to surgery are abolished. Less extensive neural blockade will not completely abolish the hormonal and metabolic changes.

In upper abdominal or thoracic surgery, it is not possible to prevent pituitary hormone responses completely, even with extensive epidural local anaesthetic blockade. In a classical study by Bromage and colleagues, epidural block up to the C6 dermatome inhibited glycaemic changes but not the increases in cortisol concentrations in response to upper abdominal and thoracic surgery.[7] Other studies confirm these findings. Many suggestions have been made to explain the failure to abolish completely the stress responses in these studies. Most of these centre around inadequate or incomplete afferent somatic and sympathetic neural blockade which allows pituitary activation and hence cortisol release from the adrenal cortex under the influence of ACTH, whilst efferent blockade of nerves to the adrenal medulla and the liver inhibits hyperglycaemic responses. Attempts were made subsequently to improve on the afferent blockade using vagal blockade, splanchnic nerve block or continuous intraperitoneal local anaesthetic, but no technique has abolished consistently the stress responses to upper abdominal or thoracic surgery.

Cardiac surgery

Perioperative thoracic epidural anaesthesia has been used successfully in the management of patients undergoing coronary artery bypass surgery.[28 46] Investigators have examined the effects of thoracic epidural analgesia on neuroendocrine secretion and on physiological variables. It is possible to prevent changes in catecholamine responses during CPB and up to 24 h after the start of cardiac surgery using thoracic epidural analgesia combined with general anaesthesia.[36] This cannot be achieved using opioid anaesthesia alone. The cortisol responses to CPB may also be attenuated using thoracic epidural analgesia, although studies show variable results.

Although there is no direct association between the attenuation of hormonal and metabolic responses and postoperative outcome, the use of thoracic epidural analgesia in cardiac surgery has many potential benefits in terms of improvements in organ function. Thoracic epidural anaesthesia provides intense analgesia, avoids the use of systemic opioids and improves postoperative pulmonary function.[28] It may reduce the incidence of thrombotic complications by decreasing the tendency towards hypercoagulability in the perioperative period.[45]

The myocardium-specific contractile protein, troponin T, is a highly specific biochemical marker of myocardial injury. Measurement of serum concentrations of the protein can be used to assess myocardial ischaemia. A recent study showed that thoracic epidural anaesthesia and general anaesthesia in cardiac surgery attenuated the myocardial sympathetic response and was associated with decreased myocardial damage as determined by less release of troponin T.[30] In medical patients, thoracic epidural analgesia has been used successfully to treat refractory angina. The sympatholytic effects of the blockade of cardiac sympathetic efferents and afferents may improve the balance of oxygen delivery and consumption. The use of thoracic epidural anaesthesia in patients with heart disease has been the subject of a recent review.[35]

Despite the potential benefits of thoracic epidural anaesthesia, there are specific cautions about the use of regional neural blockade in patients who are given anticoagulants because of the risk of epidural haematoma formation. Procedural guidelines may be used to minimize the risk of neurological complications.[3] Thoracic epidural anaesthesia is not without potential side-effects, which include possible cranial spread of the epidural block. This may lead to arm weakness, and apnoea may occur if the diaphragm is affected by blockade of nerve roots C3–C5. Testing of arm movements has been advocated to monitor cephalad spread of thoracic epidural anaesthesia.[2]

The stress response and surgical outcome

There has been a great deal of interest in the modification of the stress response with respect to the potential beneficial effects on surgical outcome. The extent to which the responses are modified depends on the choice of the analgesic techniques used. Inhibition of stress responses is greatest with neural blockade with local anaesthetics Therefore attention has focused largely on the effects of regional anaesthetic and analgesic regimens, particularly epidural blockade with local anaesthetic agents. Individual studies show that provision of analgesia using neural blockade leads to improvements in physiological variables in specific organ systems. Single investigations often cannot show benefits in morbidity and mortality because the incidence of serious complications after surgery is generally low, and the numbers of patients studied is small Meta-analysis is being used increasingly to demonstrate that regional analgesia has beneficial effects on surgical outcome.

Beneficial effects of regional analgesia

Thromboembolic complications

It is well established that regional analgesic techniques reduce the incidence of thromboembolic complications following surgery of the pelvis and lower limbs.[31] In upper abdominal procedures, there is not quite the same benefit in the incidence of thrombotic episodes.

Pulmonary function

Although it might be assumed that good analgesia with regional techniques should lead to decreased postoperative pulmonary complications, improvements in overall pulmonary outcome have not been demonstrated unequivocally. In single studies, pulmonary function has been shown to improve, and meta-analysis has found that continuous administration of epidural local anaesthetic decreases the incidence of pulmonary complications, whereas other techniques, including the use of systemic or epidural opioids, were less effective.[4]

Cardiac complications

Regional analgesia is very effective in tempering some of the cardiovascular responses to surgery which result from sympathetic activation. Whether neural blockade techniques are more beneficial in terms of overall cardiac morbidity and outcome compared with other methods of pain relief has not been established.[22, 31]

Gastrointestinal function

Continuous epidural analgesia at the thoracic level decreases paralytic ileus following abdominal procedures.[43] The use of local analgesia, or a combination of local and opioid analgesia, was more effective than either systemic or epidural opioids in preventing ileus. The elimination of ileus allows the early use of enteral nutrition which is an important factor in reducing the risk of infectious complications.[22]

Despite evidence that regional analgesia confers beneficial effects on organ function, improvements in overall postoperative morbidity and length of hospital stay have not been demonstrated conclusively. This is disappointing in view of the widespread introduction of acute pain services which consume time and resources. Of course, analgesia is provided for humanitarian reasons. Patient-controlled analgesia is popular and accepted by many patients, but has minimal effect on postoperative outcome.

Recovery from surgery

Many factors other than analgesic regimens influence recovery from major surgery and the ability of the patient to return home and resume work.[8] Surgical technique has an important role; laparoscopic procedures are associated with rapid recovery and early discharge from hospital. Other factors are also important, not least the expectations of patients and of the nursing and medical staff. Behavioural and subjective changes are part of the response to surgery. Feelings of malaise and postoperative fatigue have a strong influence on recovery from surgery and return to work. Salmon and Hall have developed a theory of postoperative fatigue which encompasses psychological and cultural mechanisms as well as physiological changes.[40] Postoperative fatigue is a complex multifactorial issue, and can be decreased in a number of ways including appropriate use of minimally invasive surgery and the avoidance of sleep disturbance. Such an 'intensive' approach is likely to be costly in terms of personnel but can be rewarded with early discharge from hospital.[22]

Kehlet advocates a 'multimodal' approach to accelerate postoperative recovery.[21] In addition to effective pain relief which allows normal function, other elements in patient management must be addressed. The use of minimally invasive surgical techniques, including laparoscopically assisted procedures, will reduce the effects of tissue injury. Postoperative nausea and vomiting and paralytic ileus should be avoided and enteral and oral feeding used. Early mobilization must be encouraged and is facilitated by good analgesia and the avoidance of tubes and drains. A rapid return to normal function has to be encouraged.

Conclusions

The stress response to surgery comprises a number of hormonal changes initiated by neuronal activation of the hypothalamic–pituitary–adrenal axis. The overall metabolic effect is one of catabolism of stored body fuels. In general, the magnitude and duration of the response are proportional to the surgical injury and the development of complications such as sepsis. Other changes also occur following surgery, notably an increase in cytokine production which is triggered locally as a tissue response to injury.

Regional anaesthesia with local anaesthetic agents inhibits the stress response to surgery and can also influence postoperative outcome by beneficial effects on organ function.

References

1 Aantaa R, Scheinin M. Alpha$_2$-adrenergic agents in anaesthesia. *Acta Anaesthesiol Scand* 1993; **37**: 1–16

2 Abd Elrazek E, Scott NB, Vohra A. An epidural scoring scale for arm movements [ESSAM] in patients receiving high thoracic epidural analgesia for coronary artery bypass grafting. *Anaesthesia* 1999; **54**: 1097–109

3 Absolom A, Pledger D, Kong A. Adrenocortical function in critically ill patients 24 h after a single dose of etomidate. *Anaesthesia* 1999; **54**: 861–7

4 Ballantyne JC, Carr DB, deFerranti S. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. *Anesth Analg* 1998; **86**: 598–612

5 Bent JM. Paterson JL, Mashiter K, Hall GM. Effects of high-dose fentanyl anaesthesia on the established metabolic and endocrine response to surgery. *Anaesthesia* 1978; **39**: 19–23

6 Blackwell TS, Christman JW. Sepsis and cytokines: current status. *Br J Anaesth* 1996; **77**: 110–17

7 Bromage PR, Shibata HR, Willoughby HW. Influence of prolonged epidural blockade on blood sugar and cortisol responses to operations upon the upper part of the abdomen and thorax. *Surg Gynaecol Obstetr* 1971; **21**: 330–35

8 Chumbley GM, Hall GM. Recovery after major surgery: does the anaesthetic make any difference? *Br J Anaesth* 1997; **78**: 347–8

9 Crozier TA, Beck D, Schlager M, Wuttke W, Kettler D. Endocrinological changes following etomidate, midazolam or methohexital for minor surgery. *Anesthesiology* 1987; **66**: 628–35

10 Cuthbertson DP. Observations on the disturbance of metabolism produced by injury to the limbs. *Q J Med* 1932; **1**: 233–46

11 Desborough JP. Physiological responses to surgery and trauma. In: Hemmings HC Jr, Hopkins PM, eds. *Foundations of Anaesthesia*. London: Mosby, 1999. 713–20

12 Desborough JP, Hall GM Modification of the hormonal and metabolic response to surgery by narcotics and general anaesthesia. *Clin Anaesthesiol* 1989; **3**: 317–34

13 Desborough JP, Hall GM. Endocrine response to surgery. In: Kaufman L *Anaesthesia Review*, Vol. 10. Edinburgh: Churchill Livingstone, 1993; 131–48

14 Desborough JP, Hall GM, Hart GR, Burrin JM. Midazolam modifies pancreatic and anterior pituitary hormone secretion after upper abdominal surgery. *Br J Anaesth* 1991; **67**: 390–96

15 Edwards R. Thyroid and parathyroid disease. *Int Anesthesiol Clin* 1997; **35**: 63–83

16 Egdahl RH. Pituitary–adrenal response following trauma to the isolated leg. *Surgery* 1959; **6**: 9–21

17 Enquist A, Brandt MR, Fernandes A, Kehlet H. The blocking effect of epidural analgesia on the adrenocortical and hyperglycaemic responses to surgery. *Acta Anaesthesiol Scand* 1977, **21**: 330–35

18 Hall GM, Young C, Holdcroft A, Alaghband-Zadeh J. Substrate mobilisation during surgery. A comparison with halothane anaesthesia. *Anaesthesia* 1978; **33**: 924–30

19 Helmy SAK, Wahby MAM, El-Nawaway M. The effect of anaesthesia and surgery on plasma cytokine production. *Anaesthesia* 1999, **54**: 733–8

20 Jameson P, Desborough JP, Bryant AE, Hall GM. The effect of cortisol suppression on the interleukin-6 and white cell responses to surgery. *Acta Anaesthesiol Scand* 1997; **40**: 123–6

21 Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997; **78**: 606–17

22 Kehlet H. Acute pain control and accelerated postoperative surgical recovery. *Surg Clin N Am* 1999; **79**: 431–43

23 Kehlet H, Mogensen T. Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme. *Br J Surg* 1999; **86**: 227–30

24 Klingstedt C, Giesecke K, Hamberger B, Janberg P-O High- and low-dose fentanyl anaesthesia, circulatory and catecholamine responses during cholecystectomy. *Br J Anaesth* 1987, **59**: 184–8

25 Lacoumenta S, Paterson JL, Myers MA, Hall GM. Effects of cortisol suppression by etomidate on changes in circulating metabolites associated with pelvic surgery. *Acta Anaesthesiol Scand* 1986; **30**: 101–4

26 Lacoumenta S, Yeo TH, Burrin JM, Bloom SR, Paterson JL, Hall GM Fentanyl and the β-endorphin, ACTH and glycoregulatory hormonal responses to surgery. *Br J Anaesth* 1987; **59**: 713–20

27 Ledingham IMA, Watt I. Influence of sedation on mortality in critically ill patients *Lancet* 1983; **i**: 1270

28 Liem TH, Hasenbos MAWM, Booij LHDJ, Gielen MJM. Coronary artery bypass grafting using two different anaesthetic effects: Part 2: Postoperative outcome. *J Cardithorac Vasc Anesth* 1992; **6**: 156–61

29 Little RA, Girolami A. Trauma metabolism—ebb and flow revisited. *Br J Intensive Care* 1999, **9**: 142–6

30 Loick HM, Schmidt C, van Aken H *et al.* High thoracic epidural anesthesia, but not clonidine, attenuates the perioperative stress response via sympatholysis and reduces the release of troponin T in patients undergoing coronary artery bypass grafting. *Anesth Analg* 1999; **88**: 701–9

31 Lui S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. *Anesthesiology* 1995; **82**: 1474–506

32 Lyons FM and Meeran K. The physiology of the endocrine system. *Int Anesthesiol Clin* 1997; **35**: 1–21

33 McDonald RK, Evans FT, Weise VK *et al.* Effect of morphine and nalorphine on plasma hydrocortisone levels in man. *J Pharmacol Exp Ther* 1959; **125**: 241–7

34 Masterson GR, Mostafa SM. Adrenocortical function in critical illness. *Br J Anaesth* 1998; **81**: 308–10

35 Meissner A, Rolf N, Van Aken H. Thoracic epidural anesthesia and the patient with heart disease: benefits, risks and controversies. *Anesth Analg* 1997; **85**: 598–612

36 Moore CM, Cross MH, Desborough JP, Burrin JM, Macdonald IA, Hall GM. Hormonal effects of thoracic extradural analgesia for cardiac surgery. *Br J Anaesth* 1995; **75**: 387–93

37 Moore RA, Allen MC, Wood PJ, Rees LH, Sear JW, Feldman D. Peroperative endocrine effects of etomidate *Anaesthesia* 1985; **40**: 124–30

38 Nicholson G, Hall GM, Burrin JM. Peri-operative steroid supplementation. *Anaesthesia* 1998; **53**: 1091–4

39 Rolf N, Mollhoff T. Epidural anaesthesia for patients undergoing coronary artery bypass grafting. *Curr Opin Anesthesiol* 1997: **10**: 17–20

40 Salmon P, Hall GM. A theory of postoperative fatigue. *J R Soc Med* 1997; **90**: 661–4

41 Schulze S, Sommer P, Bigler D *et al.* Effect of combined prednisolone, epidural analgesia, and indomethacin on the systemic response to surgery. *Arch Surg* 1992, **127** 325–31

42 Sheeran P, Hall GM. Cytokines in anaesthesia. *Br J Anaesth* 1997; **78**: 201–19

43 Steinbrook RA. Epidural anesthesia and gastrointestinal motility. *Anesth Analg* 1998; **86**: 837–44

44 Tepaske R. Immunonutrition. *Curr Opin Anaesthesiol* 1997, **10**: 86–91

45 Tuman KJ, McCarthy RJ, March R. Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. *Anesth Analg* 1991; **73**: 696–704

46 Turfrey D, Ray D, Sutcliffe NP, Ramayya P, Kenny GNC, Scott NB. Thoracic epidural anaesthesia for coronary artery bypass grafting. Effects on postoperative complications. *Anaesthesia* 1997, **52**: 1090–13

47 UKPDS group. Effect of intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risks of complications in patients with type 2 diabetes. *Lancet* 1998; **352** 837–53

48 Wagner RL, White PF Etomidate inhibits adrenocortical function in surgical patients. *Anesthesiology* 1984; **61**: 647–51

49 Wallace LK, Starr NJ, Leventhal MJ, Estafanous FG. Hyperglycaemia on ICU admission after CABG is associated with increased risk of mediastinitis or wound infection. *Anesthesiology* 1996; **85** (Suppl): A286

50 Wang C, Chan V, Yeung RT. Effects of surgical stress on pituitary testicular function. *Clin Endocrinol* 1978; **9**: 255–66

51 Woolf PD, Hamill RW, McDonald JV *et al.* Transient hypogonadotrophic hypogonadism caused by critical illness. *J Clin Endocrinol Metab* 1985; **60**: 444–450

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Malignant hyperthermia: advances in clinical management and diagnosis

P. M. Hopkins

Malignant Hyperthermia Investigation Unit, University of Leeds, Leeds, UK

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Malignant hyperthermia (MH) was the name given to a type of severe reaction under general anaesthesia that was first described in 1960.[21] Monitoring during anaesthesia at that time was based on clinical observation and physical signs, without the luxury of today's advanced equipment. The apparent features of the reactions were, therefore, dominated by a progressive pyrexia that usually led to death,[11 19 21 22] hence the name malignant hyperpyrexia or hyperthermia. The 'malignant' part of the name MH has proved useful in emphasizing the potentially fatal nature of the reaction. The 'hyperthermia' component is, perhaps, less useful because it identifies a relatively late feature of a reaction in which early intervention is important. From this point of view, it might be useful for the anaesthetist to think of MH as 'malignant hypermetabolism', because the earliest clinical features (rising end-tidal carbon dioxide concentration and tachycardia) are indicative of the metabolic nature of the reaction.

In 1988, a postgraduate educational issue of the *British Journal of Anaesthesia*[33] was devoted to a series of review articles on the subject of MH. Since then, MH research has benefited from the rapid advances in molecular genetics stemming from development of the polymerase chain reaction.[101] Elucidation of the molecular genetic basis of MH carries the prospect of presymptomatic diagnosis and a complete understanding of the aetiology of the disorder and is likely to contribute to our understanding of skeletal muscle pathology and molecular mechanisms of inhalational anaesthetics. These prospects have, however, been made less tangible by the apparent complexity of the molecular genetics of MH.[65 111] Contrary to an earlier view that DNA-based screening could be applied readily,[57] the complexity of the disorder has required a re-examination of the criteria for the clinical diagnosis of MH, refinement of *in vitro* muscle contracture tests (IVCTs) used for laboratory diagnosis and functional analysis of potential subcellular targets of the MH defect(s).[65] In this review, I will focus on these aspects of MH, along with developments in the clinical management of MH since 1988. I will not discuss the management of an MH reaction following its diagnosis, as this is essentially unchanged from earlier reviews.[33]

Clinical aspects of MH

Clinical presentation

Preoperative diagnosis

MH is a manifestation of exposure of susceptible individuals to triggering drugs. Without such exposure, it is usually impossible to identify the MH-susceptible patient unless there is a personal or family history suggestive of MH. Even then, further questioning about the details of the history will often lead to the exclusion of MH. Various musculoskeletal abnormalities, such as scoliosis, hernias or strabismus, have been associated with MH susceptibility,[10 115] but an analysis of >2500 patients tested for MH susceptibility could find no evidence to support such associations.[52] In 1988, Brownell concluded that, of the muscle diseases associated with MH, only central core disease appeared to be truly linked.[13] More recent studies have indicated that not even this link is consistent.[20 54 71]

Some syndromes with features similar to those of MH have been investigated for common aetiology. Neuroleptic malignant syndrome is discussed in the accompanying review by Adnet;[5] these patients need not be considered at risk of developing MH under anaesthesia. There is less certainty concerning those with a history of exertional heat stroke or exercise-induced rhabdomyolysis. Our group and others have demonstrated muscle abnormalities similar to those found in MH in some patients with such a history.[50 62] In our cases, the same muscle abnormality was found in relatives, but was probably not identical to that found in MH.[62] There are undoubtedly 'non-muscle' causes of heat stroke, such as obesity, concurrent viral illness or recent alcohol consumption,[25] but if these are excluded, I would advise that a patient with a history of exertional heat stroke or exercise-induced rhabdomyolysis, especially more than one episode, be investigated for MH.

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Table 1 Causes of increased serum creatine kinase concentration These can be divided into 'identifiable' and 'idiopathic' according to how easy the underlying cause is to diagnose. Hypothyroidism is by far the commonest cause, followed by myopathies

'Identifiable'	Hypothyroidism, myopathies, exercise, malignancy (always BB isoenzyme), denervation syndromes, myocardial infarction, rhabdomyolysis (trauma, drugs)
'Idiopathic'	Malignant hyperthermia susceptibility, Duchenne dystrophy carriers, idiopathic paroxysmal rhabdomyolysis, haemolytic syndromes, previous neuroleptic malignant syndrome

Table 2 Clinical features of malignant hyperthermia. The changes are grouped according to their timing of onset in the reaction. The time periods (early, succeeding and late) cannot be quantified because they vary greatly between patients, they do indicate a consistent temporal relationship in the onset of clinical features Features in brackets may have their onset at any stage of the reaction. SV=spontaneous ventilation

Timing	Clinical signs	Changes in monitored variables	Biochemical changes
Early	Sustained jaw rigidity after succinylcholine		
	Tachypnoea (SV)	Increased minute ventilation (SV)	
	Rapid exhaustion of soda lime	Rising end-tidal carbon dioxide	Increased Pa_{CO_2}
	Hot soda lime canister		
	High pulse rate	Tachycardia	Decreased pH
	(Irregular pulse)	(Ventricular ectopics)	(Increased [K^+])
		(Peaked T waves on ECG)	
Succeeding	Patient hot to touch	Rising core body temperature	
	Cyanosis	Falling Sp_{O_2}	Decreased Pa_{O_2}
	Dark blood in wound		
	(Irregular pulse)	(Ventricular ectopics)	(Increased [K^+])
		(Peaked T waves on ECG)	
Late	Generalized muscle rigidity		
	Prolonged bleeding		
	Dark urine		Increased creatine kinase, myoglobinuria
	Oliguria		
	(Irregular pulse)	(Ventricular ectopics)	
		(Peaked T waves on ECG)	(Increased [K^+])
	Death		

Table 3 Differential diagnoses of a suspected malignant hyperthermia reaction

- Inadequate anaesthesia or analgesia
- Inappropriate breathing circuit, fresh gas flow or ventilation
- Infection or sepsis
- Tourniquet ischaemia
- Anaphylaxis
- Phaeochromocytoma
- Thyroid storm
- Cerebral ischaemia
- Other muscle diseases

Occasionally, a 'routine' preoperative biochemical screen will reveal an increased raised serum creatine kinase concentration in an apparently asymptomatic patient. This could be indicative of MH, but investigation for MH need be done only if more common causes of creatine kinase elevation and uncommon causes requiring less invasive diagnostic techniques than MH (Table 1) are excluded.

Presentation during anaesthesia

There is no clinical feature that is specific for MH. Diagnosis depends on a knowledge of features that can occur during an MH reaction (Table 2), recognition of these features occurring in a pattern (including temporal relationships between individual manifestations) consistent with an evolving MH reaction, and exclusion of other causes of these clinical features (Table 3). Early diagnosis is important, as prompt, appropriate treatment is associated with the best outcome.

(i) Masseter spasm. In the absence of a family history of MH, the first indication that an individual may be susceptible to the condition is the development of an exaggerated initial response to succinylcholine, i.e. an increase in tension of the jaw muscles.[17] If sufficiently sensitive measuring equipment is used, jaw stiffness after administration of succinylcholine can be detected in most individuals.[81] It is often more pronounced in children.[123] When the jaw stiffness is severe, and especially when it is prolonged, the condition is called masseter spasm. Doubt has been expressed as to the validity of masseter spasm as an indicator of potential MH susceptibility,[86 122] but this doubt was based on a false premise.[33 60] Interestingly, several of the patients included in the report by Littleford and colleagues[86] have been proven subsequently to be susceptible to MH. A further illustration of the need to consider a patient developing masseter spasm following succinylcholine as potentially susceptible to MH is presented by Ramirez and colleagues.[109] These workers reported the case of a trauma victim in whom tracheal intubation in the accident and emergency department was difficult because of increased resistance to mouth opening following the use of succinylcholine. Anaesthesia was maintained using an infusion of propofol during transfer to the CT scanner and from there to the operating theatre. Once in the operating theatre, for fixation of a humeral fracture, isoflurane was substituted for propofol and subsequently the typical metabolic features of MH developed.[109]

(ii) Hypermetabolism. MH occurs because the triggering drugs cause an imbalance in Ca^{2+} homeostasis within skeletal muscle cells.[87 113] The increased intracellular Ca^{2+} concentration stimulates metabolism both directly, through activation of phosphorylase to increase glycolysis, and indirectly, because of an increased demand for ATP production. ATPases are important components of myofilament relaxation and the Ca^{2+} sequestration pumps of the sarcoplasmic reticulum and sarcolemma. Metabolic stimulation leads to increased carbon dioxide production (tachypnoea and increased end-tidal carbon dioxide concentration) and early lactic acidosis (possibly related to acute intracellular inorganic phosphate deficiency). The resulting mixed respiratory and metabolic acidosis stimulates sympathetic outflow, leading to tachycardia. In humans, changes in arterial pressure are not usually marked in the early phases of MH; this may reflect opposing effects of increased sympathetic drive and locally mediated peripheral vasodilation secondary to tissue acidosis. Increasing body temperature is a relatively late indicator of the hypermetabolic response.[109]

(iii) Muscle rigidity and breakdown. Generalized muscle rigidity can occur in association with masseter spasm following succinylcholine and usually indicates MH susceptibility.[31] As with masseter spasm, it resolves spontaneously, usually within 5 min. A more insidious development of generalized skeletal muscle rigidity during maintenance of anaesthesia with potent inhalational anaesthetics is a sinister feature of MH. It indicates that the ability of the muscle to produce ATP, a function crucial to the reversal of the MH process even if Ca^{2+} release can be halted, is almost exhausted. Sustained rigor also restricts the circulation to the muscle beds, resulting potentially in accumulation of toxic metabolic products and heat, and failure of delivery of oxygen and therapeutic agents to the muscle.

Evidence of rhabdomyolysis can usually be obtained by measuring serum creatine kinase and urinary (or serum) myoglobin concentrations. The time-course of changes in the serum concentrations of these proteins has been described.[80] The magnitude of these changes following MH reactions is, however, quite variable. In some cases, the changes may be indistinguishable from those resulting from surgery,[79] but in others, especially when succinylcholine and a potent inhalational anaesthetic have been used in combination, the creatine kinase concentration may be a thousand times normal. Rhabdomyolysis also leads to extrusion of K^+ from the damaged muscle. Hyperkalaemia and sympathetic stimulation are the main causes of cardiac arrhythmias in MH.

Postoperative presentations

The onset of MH varies in its speed. In some cases, metabolic stimulation will be evident clinically within 10 min of the administration of a potent inhalational anaesthetic; in others, several hours may elapse. It is plausible that the speed of onset reflects the rate of increase in intracellular Ca^{2+} concentration, which will depend on the particular drug used, the concentration of the drug in the muscle and any number of physiological variables that dictate the efficiency of Ca^{2+} homeostatic processes in the individual. Considered together with the complete range of duration of surgical procedures, this variability in timing of onset and rate of development of MH dictates that a procedure may conclude just before the symptoms of MH become apparent. In this situation, the reaction will progress while trigger drug concentrations in the muscle remain above a threshold value. It is possible that lower concentrations of trigger drugs are needed to maintain a reaction than to initiate it because an increased intracellular Ca^{2+} concentration stimulates sarcoplasmic reticulum Ca^{2+} release through the mechanism known as Ca^{2+}-induced Ca^{2+} release.[73 129] Similarly, if very high intracellular Ca^{2+} concentrations are reached, Ca^{2+}-induced Ca^{2+} release may sustain an MH reaction even when the trigger drug has been eliminated, especially if Ca^{2+} sequestration is compromised by a reduced capability for ATP production. This is probably why recrudescence of signs can occur after their initial control.

MH reactions that begin soon before or after the end of surgery do, however, present with the same features as intraoperative reactions. This is important because it means that postoperative pyrexia, in the documented absence of tachypnoea, raised end-tidal partial pressure of carbon dioxide and tachycardia, is *not* indicative of MH.[53] It is important to stress that MH cannot be excluded as the cause of postoperative pyrexia if records of anaesthesia and the immediate postoperative period do not detail variables indicative of hypermetabolism. Occasionally, no metabolic features of an MH reaction are recognized during the perioperative period (they may, for example, be attributed to sepsis) and the patient will present 2–4 days after the operation in acute renal failure secondary to rhabdomyolysis.[12]

Clinical diagnosis

None of the clinical features of MH is specific to MH (Table 2) and a variety of differential diagnoses exists (Table 3). Several attempts have been made to analyse clinical features of MH reactions for their use in diagnosis.[31 49 76 78] Each of these studies used a different approach and three will be discussed further. Ellis and colleagues,[31] based on a suggestion by Ording and Ranklev (see ref. 52), defined eight categories of clinical presentation. Three of these included reactions that were predominantly metabolic, but of different severity; a further three categories were for masseter spasm, either alone, with other 'muscle' features (high creatine kinase, generalized muscle rigidity) or with metabolic signs; the other categories were unexplained anaesthetic death or cardiac arrest and 'other presentations', e.g. postoperative pyrexia or renal failure.[31] Four hundred and two index patients were assigned to these categories; for each category, the proportion of patients diagnosed as susceptible to MH using IVCTs was calculated. This approach has proved useful in providing a rough estimate of the likelihood of MH (and the need for definitive testing) in patients who have experienced an adverse reaction which was thought to be MH Further use of these data is limited because they were inevitably dependent on contemporary anaesthetic practice and the referral pattern to our unit. For example, I suspect that patients with lesser degrees of masseter spasm are referred now, compared with 15–20 years ago, because of the prevalence of articles on this subject in the intervening period.

Hackl and colleagues[49] also compared results of IVCTs with clinical signs in index cases, but with a more sophisticated statistical approach. They generated logistic regression models in an attempt to predict MH susceptibility. However, the best model could correctly classify only 78% of subjects, highlighting the difficulty in predicting MH susceptibility from clinical features.

Rather than analysing data from a sample of patients, Larach and colleagues used the Delphi process to generate iteratively a consensus clinical grading scale for MH.[78] Eleven experts responded to a series of questionnaires in which they were asked to score the relative importance of potential clinical indicators of MH, with feedback and anonymous comments from the other members of the expert panel. Scoring was ultimately used to generate a qualitative indication of likelihood of MH susceptibility.[78] This study has proved invaluable in validating the laboratory diagnostic techniques for MH susceptibility[7 103] because 'true' diagnosis of MH susceptibility obtained using the 'almost certain' descriptor of the clinical grading scale[78] was derived totally independently of contracture test results. However, the clinical grading scale can be criticized. First, no weighting is given to the temporal relationship of events, which can be used to exclude MH in some situations. Second, the score will be influenced greatly by missing data. Most importantly, the scores and rules for their application are somewhat ambiguous, leading to considerable variability in scoring, even among the 11 experts used to generate the clinical grading scale.[78]

Pharmacological triggers of malignant hyperthermia

The potent inhalational anaesthetic drugs are the most commonly implicated pharmacological triggers of MH. Indeed, there are no verified cases of death from MH where a potent inhalational anaesthetic has not been used. There remains uncertainty over some groups of drugs because of the potential limitation in extrapolating *in vitro* data to exclude a drug, that has been implicated on the basis of a clinical report, as a trigger. Over the past 30 years, many groups of drug have been implicated when one of their number was used as part of a combination of drugs providing anaesthesia for patients who subsequently developed an MH reaction during surgery. The situation is complicated further by a lack of verification that the clinical reaction was a true MH response rather than being caused by other factors, such as sepsis, inadequate anaesthesia or analgesia or, more rarely, thyrotoxicosis or phaeochromocytoma.

Potent inhalational anaesthetic drugs

Although MH was not recognized until the introduction of halothane, it is likely that the classical anaesthetic vapours, diethyl ether and chloroform, in addition to other now unused ether derivatives, accounted for many fatal cases of MH.[22 55] *In vitro* studies have demonstrated that ether and chloroform cause contracture in MH muscle (unpublished observations) and it is probable that these early MH reactions went unnoticed, because of the lack of routinely available monitoring systems and, perhaps, because death under anaesthesia was relatively common. Of the contemporary potent inhalational drugs, halothane is the most potent at inducing sustained contraction in isolated muscle strips from MH patients. The frequency of implication of the individual volatile drugs as triggers in the clinical setting reflects, however, the frequency of their use in anaesthesia, with isoflurane being the most commonly implicated trigger in the UK at present. Sevoflurane, which has only recently been introduced into European and North American practice, has been used for several years in Japan and has triggered MH reactions in several reported cases.[27 105] The other recently introduced drug, desflurane, has also been reported to cause MH.[6 41 96]

In vitro challenge of skeletal muscle with halothane has formed the basis of diagnostic testing for MH for nearly 30 years.[28 30] Similar *in vitro* challenge tests have been used with other drugs to test their potential for triggering human MH.[39] When conducting such tests, it is vital that appropriate concentration ranges of the test drug are used. This is relatively easy with potent inhalational drugs because the partial pressure of the agent used to produce clinical anaesthesia is easily extrapolated and this can be reproduced in the laboratory. With other drugs, account must be taken of the volume of distribution and, especially, the plasma protein binding when calculating the active clinical concentration by extrapolation from the clinical dose range.

Neuromuscular blocking drugs

As discussed above, masseter spasm after the use of succinylcholine is often the first indication that a patient may be susceptible to MH. *In vitro* experiments demonstrate that succinylcholine will cause an increase in intracellular

Ca^{2+} concentration in normal muscle[59] and it seems reasonable to postulate that this Ca^{2+} release is exaggerated in MH muscle. Recent research using skinned muscle fibre preparations from human masseter muscle indicates why the increase in tone following succinylcholine is most pronounced in this one group of muscles.[4] It appears that the masseter muscle contains a remarkably high proportion of type I fibres. The myofilaments of type I fibres are more sensitive to Ca^{2+} than those of type II fibres[112] and so any increase in intracellular Ca^{2+} ion concentration in type I fibres is likely to produce greater contractile activity than a similar increase in type II fibres. This may be compounded by an increased sensitivity of the sarcoplasmic reticulum Ca^{2+} release channel in type I fibres to factors that promote Ca^{2+} release, such as caffeine and Ca^{2+} itself.[4]

There is debate about whether succinylcholine alone produces the metabolic features of MH, but a recent well documented case demonstrates that this indeed does occur, albeit to a mild degree.[80] What is clear is that administration of succinylcholine following an inhalation induction of anaesthesia with a volatile anaesthetic drug is more likely to produce masseter spasm and to produce the most rapid development of a severe MH reaction.

Non-depolarizing neuromuscular blocking drugs are now generally accepted to be safe in MH. Some authorities recommend that tubocurarine be avoided in MH-susceptible individuals as this drug has been shown to cause a small depolarization of denervated skeletal muscle[45] and was implicated in an early case report.[12] With the decreasing clinical usage of tubocurarine, this point is, however, becoming of only historical interest.

Phenothiazines

Phenothiazines were implicated in some of the early reports of MH as they were one of several groups of drugs given to patients who developed suspected MH reactions. There was even a case report of an MH reaction after premedication with trimeprazine before general anaesthesia was instated.[100] It was because of these reports that phenothiazines and related drugs, including other major and minor tranquillizers, entered the literature as possible triggers of MH. Now that they have entered the literature, it has proved difficult to discount completely the possibility that these drugs do indeed trigger MH. It is most likely that they are not triggers of MH. Several arguments can be put forward to support this view. In many of the case reports implicating phenothiazines, potent inhalational anaesthetics were also used. There is also some doubt as to whether some of the reactions reported as MH were true MH responses; this includes the report of MH following premedication with trimeprazines.[100] No case of MH following phenothiazine use alone has been verified by contracture test diagnosis on the patient concerned. Phenothiazines have anticholinergic actions, including antidiaphoresis, which can—especially in children—limit heat loss to such an extent that the body temperature will increase. MH has been confused with neuroleptic malignant syndrome,[48] which has similar clinical features to MH (pyrexia, muscle rigidity and rhabdomyolysis) but develops over 24–72 h and results from the central antidopaminergic effects of major tranquillizer drugs.[3 5]

In vitro studies of the effect of phenothiazines demonstrate that they can induce muscle contracture, but this occurs at concentrations far beyond those achieved with therapeutic concentrations of the drug.[2] These studies, however, have not dispelled completely the concern over phenothiazines and related drugs in MH. Perhaps the most reassuring factor in the use of phenothiazines and other major and minor tranquillizers in MH-susceptible patients is that there have been no reports of MH associated with usage of the drugs outside anaesthetic practice. Given the widespread use of these drugs and an incidence of MH of one in 8500 in the population, it would be anticipated that several cases should have occurred if the drugs were true triggers of MH.

Intravenous anaesthetic drugs

There is now vast experience of the safe use of the more commonly used intravenous anaesthetic drugs in patients who are known to be susceptible to MH. This includes the three most commonly used agents in current clinical practice, thiopental, etomidate and propofol. There was concern over the capacity of ketamine to induce a MH response, but the tachycardia and hypertension observed in MH-susceptible pigs and humans is probably a result of the usual sympathomimetic response to ketamine. Indeed, there is evidence that ketamine will in fact reduce Ca^{2+} release in skeletal muscle.[94]

Local anaesthetics

Ester local anaesthetics, specifically procaine, formed part of the limited treatment regimen for an MH reaction before the introduction of dantrolene,[51 58] although its value was questioned.[18 98] That ester local anaesthetics have some efficacy in MH is a result of their ability to reduce calcium release from the sarcoplasmic reticulum of skeletal muscle.[128] It is probably also for this reason that direct injection of ester local anaesthetics into myotonic muscles can relieve the myotonia.[61] On the other hand, early experiments with lidocaine, an amide local anaesthetic drug, showed that it induced *in vitro* contracture in skeletal muscle.[9] This led to amide local anaesthetics becoming contraindicated in MH-susceptible individuals as potential triggering drugs. It was soon realized, however, that the initial *in vitro* studies with lidocaine used inappropriately high concentrations of the drug, which could induce *in vitro* contracture even in normal muscle. Subsequent studies in pigs susceptible to porcine stress syndrome demonstrated that lidocaine did not trigger a reaction.[127] More recent experiments with mepivacaine indicate that MH muscle is perhaps more sensitive to the contracture-inducing effects of amide local anaesthetics (E. Hartung, personal communication), but again the concentration of mepivacaine required to produce contracture in MH muscle is still far in excess of that achieved systemically in normal clinical practice.

We now use femoral nerve block with amide local anaesthetic to provide analgesia for the diagnostic muscle biopsy of patients potentially susceptible to MH as our standard practice in the UK MH Investigation Unit in Leeds. Initially, lidocaine and bupivacaine were used. Lidocaine has since been replaced by prilocaine, which has a higher therapeutic index for neurological and cardiac complications. We have used prilocaine 5 mg kg^{-1} in >1000 patients who proved to be susceptible to MH. This dose of prilocaine is sufficient to cause clinically apparent methaemaglobinaemia in some patients[8] and, in one case, inadvertent intravascular injection led to fitting, but there has been no indication of triggering of MH in any patient.

Other drugs

As alluded to earlier, anticholinergic drugs can exacerbate pyrexia because of their anti-diaphoretic action. This may make treatment of an MH reaction triggered by, for example, potent inhalational anaesthetics, more difficult but should not preclude their use in MH-susceptible individuals.[102] There has also been uncertainty over the use of catecholamines and other sympathomimetic drugs which has arisen in the context of conflicting evidence from studies in pigs with porcine stress syndrome (porcine MH).[26 46 47 85 88] As porcine stress syndrome is triggered by stress, whereas human MH is not, it would seem reasonable to assume that MH-susceptible humans would be less likely to respond abnormally to catecholamines than are pigs. The lack of response in pigs with porcine stress syndrome to intravenous infusion of norepinephrine[46] is reassuring from the human perspective.

One group of drugs that could trigger MH are those having similar structure or actions to caffeine, one of the compounds used for *in vitro* diagnosis of the condition.[35] Theophylline and aminophylline do indeed cause *in vitro* contracture in muscle and, at lower concentration, in muscle from MH individuals (unpublished observations), but these concentrations are several times greater than those achieved with therapeutic use. Caffeine and other methylxanthines are non-specific phosphodiesterase inhibitors and it is possible that this effect contributes to the sensitivity of MH muscle to caffeine. Specific inhibitors of type III phosphodiesterase have gained a place in the management of heart failure and as inotropes in cardiac surgery. One of these, enoximone, has been evaluated for its effect on isolated human muscle from normal and MH-susceptible individuals.[34] As with the methylxanthines, enoximone produced a concentration-dependent contracture, with the dose–response curve shifted to the left in muscle from MH-susceptible individuals. The minimum concentration for contracture development was 100 times greater than has been measured with clinical use of enoximone.[34]

Advances in the laboratory diagnosis of MH

The two widely used protocols for the diagnosis of MH susceptibility using IVCTs with living skeletal muscle[35 36 75] both use separate exposure to halothane and to caffeine. The protocol of the North American MH Group also allowed for a combined caffeine–halothane test,[75] but this has been largely abandoned because of a high incidence of false-positive results.[32 77] The separate-exposure halothane and caffeine tests also have their imperfections. Results of IVCT that have been done on patients with a low risk of MH ('controls') suggest a false-positive rate of approximately 6% using the European protocol[103] and 9% using the North American protocol.[77] In results from the Leeds MH Investigation Unit, 14% of patients with an abnormal response to halothane reacted normally to caffeine, indicating that the caffeine test lacks total sensitivity. A report of complete failure of the European MH Group protocol to detect cases of MH susceptibility,[70] however, has not stood up to close scrutiny, both in terms of strict application of the test protocol and the clinical diagnoses of MH.

The halothane and caffeine IVCTs have proved satisfactory for clinical diagnostic purposes over the past 30 years. The lack of specificity of both tests and the lack of sensitivity of the caffeine test do, however, pose problems for genetic studies of MH where accurate phenotyping is essential. One approach to improving accuracy is to assess other drugs that induce *in vitro* muscle contracture for their ability to distinguish MH-susceptible from normal muscle. Two drugs, ryanodine and chlorocresol, have shown real potential.

Ryanodine

Ryanodine, formerly used as an insecticide, was shown in the late 1950s to cause time- and dose-dependent contractures of normal rabbit and rat skeletal muscle.[114] It was subsequently suggested that ryanodine could be used to produce an animal model for MH.[16 38] Unfortunately, this idea was not developed further and ryanodine was neglected by MH researchers until the late 1980s when it was described as having great affinity for the sarcoplasmic reticulum calcium release channel.[91] Indeed, ryanodine was so important in the purification and characterization of this calcium release channel that it became known as the ryanodine receptor protein.[15] It was then not long before the ryanodine receptor protein was suggested to be the site of the MH defect because [^{3}H]ryanodine was shown to have greater affinity for the protein from pigs with porcine stress syndrome than for that from normal pigs.[97]

With the publication of these studies it seemed clear that ryanodine was worth investigating for its effect on human MH muscle. Following initial dose-finding studies using rat diaphragm and human tissue, a protocol was devised for a pilot study to compare responses to ryanodine of muscle from MH-susceptible and normal individuals.[63] The results of the pilot study suggested that the ryanodine contracture test could be specific for MH. It was also interesting that muscle from two patients with equivocal responses to the standard halothane and caffeine tests (MHE) behaved in a similar way to that of the susceptible patients.[63] A larger series of patients was included in a further study using a refined ryanodine application protocol.[64] The results again gave credence to the possibility that ryanodine contracture testing was able to distinguish MH-susceptible from normal patients. Furthermore, they appeared to identify two populations within the MHE group, which suggested the test had the potential to distinguish positive and negative patients within this group—a great asset for future genetic analyses.[64]

Similar results were reported subsequently by other groups,[56 82 124 125] but each group was using its own protocol. Differences in the protocols included the purity of the ryanodine used, the concentrations of ryanodine applied, whether a bolus or incremental addition of ryanodine was used and the criteria for determining the end-points of the test. Although most studies reported good discrimination of MH-susceptible and normal patients, it was very difficult to compare the results between groups.

At its meeting in Padua in 1993, the European MH Group agreed the necessity for a common protocol for the ryanodine contracture test if the compound was to be evaluated as an additional test drug. There was a need to confirm that ryanodine could distinguish between MH-susceptible and normal in a large series of patients and that the test was reproducible between laboratories. The results of the multicentre evaluation of this protocol were published in 1998.[67] The study enabled the determination of cut-off values that can be used to categorize a ryanodine contracture test response as MH-susceptible or normal with varying degrees of probability.

There were statistical differences found in ryanodine responses between several centres, but in the majority of cases these were not large enough to compromise the use of common parameters for discriminating between 'normal' and 'abnormal' ryanodine contracture responses.[67] An analogous situation exists with the diagnostic halothane and caffeine tests. In these tests, common threshold concentrations of halothane and caffeine are successfully used by all centres, but the size of contracture developed at threshold concentrations does vary between centres. The ryanodine contracture test results of one centre, however, were markedly different from those of the other centres. These differences were so marked that, at the time of publication of the paper,[67] they raised a great deal of uncertainty about the use of the ryanodine contracture test. It has transpired subsequently that the centre producing the disparate results had been stimulating the muscle at 10 times the agreed rate. The study of Sudo and Nelson[118] demonstrated how this can influence responses to ryanodine. The North American MH Group have subsequently adopted the European MH Group protocol for the ryanodine contracture test for the use of their members who wish to use a ryanodine test.

Future use of the ryanodine contracture test

We have examined the predictive probability of the various contracture tests in determining MH susceptibility.[66] Interestingly, the rank order of correlation with MH diagnosis of the four tests studied was ryanodine > dynamic halothane > static halothane > caffeine test. Although we would not advise abandoning tests with halothane and caffeine, our results suggest that an additional ryanodine contracture test is of value. Furthermore, in the same paper,[66] we demonstrated how ryanodine contracture test results could be combined with results of the other tests in a mathematical model to produce a sensitive and specific estimate of the probability of an individual being truly MH susceptible. This has potential application in producing a quantitative phenotype for genetic analyses which would enable the inclusion of MHE patients in such analyses. A further use for the ryanodine contracture test is in comparison of results produced by the two major protocols for IVCT, those of the North American and European MH Groups.[40]

Chlorocresol

4-Chloro-*m*-cresol (4-CmC) is used as a preservative in some pharmaceutical preparations of, for example, insulin, heparin and succinylcholine. It affects the Ca^{2+} release channel of skeletal muscle sarcoplasmic reticulum and causes time- and dose-dependent muscle contracture.[119] Early studies, each using a different protocol, have shown promise similar to ryanodine.[44 104 119 126] Multicentre evaluation of a common protocol is in progress.

Molecular genetics of MH

Early genetic linkage studies found linkage to chromosome 19q12.1-13.2,[90 95] the locus of the ryanodine receptor gene (*RYR1*), the gene encoding the skeletal muscle sarcoplasmic reticulum Ca^{2+} release channel.[89] As further families have been investigated, though, it has become apparent that the molecular genetics of MH are more complex.[65] To date, fewer than 60 families worldwide have proved large enough to provide informative genetic data. These data have demonstrated genetic heterogeneity[23 83] with the results from 30–80% of families consistent with linkage to *RYR1*. In families where linkage data have excluded the *RYR1* locus, further linkage analysis to loci of physiologically plausible candidate genes, such as the subunits of the dihydropyridine (DHPR) membrane Ca^{2+} channel, have been carried out. No linkage has been verified (but see references 72 and 84) to the β or γ subunits,[68 116] but one German pedigree is significantly linked to the region of the gene encoding the $\alpha 2/\delta$ subunit; this locus is found on chromosome 7q.[69] A genomic search identified linkage in a French family to the gene encoding the $\alpha 1$ DHPR subunit on chromosome 1q[110] and a mutation in this gene was subsequently found in MH-susceptible members of this family.[99]

Genomic searches have identified two further loci, on chromosomes 3q[117] and 5p,[110] to which MH susceptibility was linked in one family in each case. Subsequent studies using other families have failed to find other pedigrees in which MH susceptibility is linked to these loci.

Developments have also taken place in the search for mutations of *RYR1* that may be causative of MH. The first human mutation was found[43] following the discovery that an arginine to cysteine substitution in amino acid position 614 of *RYR1* in pigs was associated with porcine stress syndrome.[42] The mutation underlying this substitution, C1840T, in humans has been found in 14 out of 333 susceptible individuals from separate MH pedigrees in Europe (European MH Group, unpublished data). Fifteen further mutations have been found in one or more MH families.[74 92 93 106–108] Of these mutations, the commonest is the G1021A mutation, which has been found in 19 out of 298 susceptible individuals screened in Europe (European MH Group, unpublished data). When the extended pedigrees of these families are examined, however, there is discordance between inheritance of the mutation and MH susceptibility in five families (European MH Group, unpublished data). There is a similar situation with the C1840T mutation[24 37] where discordance is present in four out of 14 families investigated (European MH Group, unpublished data). Our study of a large UK pedigree[1] in which the G1021A mutation is found in only seven of 12 MH-susceptible individuals, points to a second underlying genetic abnormality causing MH in this family. While it is difficult to envisage that the mutations so far described in *RYR1* do not play a role in MH, and while this is supported by functional expression studies,[120 121] there is such a high rate of discordance of the two more common mutations that these may well be only modifying factors in expression of the disorder.

The complexity of the molecular genetics of MH described above precludes DNA-based diagnosis at present, especially when one considers the possibility of one gene defect being associated with susceptibility in only a proportion of individuals and another, as yet unidentified, defect being causative of the condition. This is complicated further by the well-established presence of genetic heterogeneity. The first step in a DNA-based diagnosis, therefore, will rely on initial identification of the abnormality, or abnormalities, causing MH in individual pedigrees. It is likely that the first reliable DNA-based diagnoses will be carried out in individuals from families that have been extensively investigated by both IVCT phenotyping and linkage analysis followed by mutation screening.

References

1 Adeokun AM, West SP, Ellis FR *et al.* The G1021A substitution in the RYR1 gene does not cosegregate with malignant hyperthermia susceptibility in a British pedigree. *Am J Hum Genet* 1997; **60**: 833–41

2 Adnet PJ, Krivosic-Horber RM, Adamantidis MM *et al.* The association between the neuroleptic malignant syndrome and malignant hyperthermia. *Acta Anaesthesiol Scand* 1989; **33**: 676–80

3 Adnet PJ, Reyford H, Krivosic-Horber RM Neuroleptic malignant syndrome. In: Hopkins PM, Ellis FR, eds. *Hyperthermic and Hypermetabolic Disorders.* Cambridge: Cambridge University Press, 1996, 223–38

4 Adnet PJ, Reyford H, Tavernier BM *et al.* In vitro human masseter muscle hypersensitivity: a possible explanation for increase in masseter tone. *J Appl Physiol* 1996; **80**: 1547–53

5 Adnet PJ Lestavel P, Krivosic-Horber R. Neuroleptic malignant syndrome. *Br J Anaesth* 2000, **85**: 129–35.

6 Allen GC, Brubaker CL Human malignant hyperthermia associated with desflurane anesthesia. *Anesth Analg* 1998; **86**: 1328–31

7 Allen GC, Larach MG, Kunselman AR. The sensitivity and specificity of the caffeine–halothane contracture test: a report from the North American Malignant Hyperthermia Registry The North American Malignant Hyperthermia Registry of MHAUS. *Anesthesiology* 1998; **88**: 579–88

8 Bellamy MC, Hopkins PM, Halsall PJ, Ellis FR. Study into the incidence of methaemoglobinaemia after prilocaine 3·1 block. *Anaesthesia* 1992, **47**: 1084–5

9 Bianchi CP, Bolton TC. Action of local anesthetics on coupling systems in muscle. *J Pharmacol Exp Ther* 1967; **157**: 388–405

10 Britt BA. Preanesthetic diagnosis of malignant hyperthermia. *Int Anesthesiol Clin* 1979; **17**. 63–96

11 Britt BA, Gordon RA. Three cases of malignant hyperthermia with special consideration of management. *Can Anaesth Soc J* 1969; **16**: 99–105

12 Britt BA, Webb GE, LeDuc C. Malignant hyperthermia induced by curare. *Can Anaesth Soc J* 1974; **21**: 371–5

13 Brownell AK. Malignant hyperthermia. relationship to other diseases. *Br J Anaesth* 1988; **60**: 303–8

14 Burns AP, Hopkins PM, Hall G, Pusey CD Rhabdomyolysis and acute renal failure in unsuspected malignant hyperpyrexia. *Q J Med* 1993; **86**: 431–4

15 Campbell KP, Coronado R, Smith JS, Imagawa T. Purified ryanodine receptor from skeletal muscle sarcoplasmic reticulum is the Ca^{2+} -permeable pore of the calcium release channel. *J Biol Chem* 1987; **262**: 16636–43

16 Casson H, Downes H. Ryanodine toxicity as a model of malignant hyperthermia. In: Aldrete JA, Britt BA, eds. *Malignant Hyperthermia.* New York: Grune & Stratton, 1978; 3–10

17 Christian AS, Ellis FR, Halsall PJ. Is there a relationship between masseteric muscle spasm and malignant hyperpyrexia? *Br J Anaesth* 1989; **62**: 540–4

18 Clarke IM, Ellis FR An evaluation of procaine in the treatment of malignant hyperpyrexia *Br J Anaesth* 1975, **47**: 17–21

19 Cullen WG. Malignant hyperpyrexia during general anaesthesia; a report of two cases. *Can Anaesth Soc J* 1966; **13**: 437–43

20 Curran JL, Hall WJ, Halsall PJ et *al.* Segregation of malignant hyperthermia, central core disease and chromosome 19 markers. *Br J Anaesth* 1999; **83**: 217–22

21 Denborough MA, Lovell RRH. Anaesthetic deaths in a family. *Lancet* 1960; **ii**: 45

22 Denborough MA, Foster JFA, Lovell RRH, Maplestone DA, Villiers JD. Anaesthetic deaths in a family. *Br J Anaesth* 1962, **34**: 395–6

23 Deufel T, Golla A, Iles D *et al.* Evidence for genetic heterogeneity

of malignant hyperthermia susceptibility. *Am J Hum Genet* 1992; **50**: 1151–61

24 Deufel T, Sudbrak R, Feist Y *et al* Discordance, in a malignant hyperthermia pedigree, between *in vitro* contracture-test phenotypes and haplotypes for the *MHS1* region on chromosome 19q12-13.2, comprising the C1840T transition in the *RYR1* gene. *Am J Hum Genet* 1995; **56**: 1334–42

25 Dickinson JG. Exertional heat stroke: predisposing factors, clinical features, treatment and prevention. In: Hopkins PM, Ellis FR, eds. *Hyperthermic and Hypermetabolic Disorders*. Cambridge: Cambridge University Press, 1996; 20–41

26 Dinsmore J, Hall GM. Porcine stress syndrome. In: Hopkins PM, Ellis FR, eds. *Hyperthermic and Hypermetabolic Disorders*. Cambridge: Cambridge University Press, 1996; 202–20

27 Ducart A, Adnet P, Renaud B, Riou B, Krivosic-Horber R. Malignant hyperthermia during sevoflurane administration. *Anesth Analg* 1995; **80**: 609–11

28 Ellis FR, Harriman DG. A new screening test for susceptibility to malignant hyperpyrexia. *Br J Anaesth* 1973; **45**: 638

29 Ellis FR, Smith G. Symposium on malignant hyperthermia. *Br J Anaesth* 1988; **60**: 251–319

30 Ellis FR, Keaney NP, Harriman DG *et al*. Screening for malignant hyperpyrexia. *BMJ* 1972; **iii**: 559–61

31 Ellis FR, Halsall PJ, Christian AS. Clinical presentation of suspected malignant hyperthermia during anaesthesia in 402 probands. *Anaesthesia* 1990; **45**: 838–41

32 Ellis FR, Halsall PJ, Hopkins PM. Is the "K-type" caffeine–halothane responder susceptible to malignant hyperthermia? *Br J Anaesth* 1992; **69**. 468–70

33 Ellis FR, Hopkins PM, Halsall PJ, Christian AS Masseter muscle spasm and the diagnosis of malignant hyperthermia susceptibility. *Anesth Analg* 1992; **75**: 143–6

34 Enright SM, Hopkins PM, Halsall PJ, Ellis FR. Can enoximone trigger malignant hyperthermia? *Br J Anaesth* 1997; **78**: 460P

35 European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia susceptibility. *Br J Anaesth* 1984; **56**. 1267–9

36 European Malignant Hyperpyrexia Group Laboratory diagnosis of malignant hyperthermia susceptibility (MHS). *Br J Anaesth* 1985; **57**: 1038

37 Fagerlund TH, Ording H, Bendixen D, Islander G, Ranklev Twetman E, Berg K. Discordance between malignant hyperthermia susceptibility and *RYR1* mutation C1840T in two Scandinavian MH families exhibiting this mutation. *Clin Genet* 1997; **52**: 416–21

38 Fairhurst AS, Hamamoto V, Macri J. Modification of ryanodine toxicity by dantrolene and halothane in a model of malignant hyperthermia. *Anesthesiology* 1980; **53**: 199–204

39 Fletcher JE, Rosenberg H, Lizzo FH. Effects of droperidol, haloperidol and ketamine on halothane, succinylcholine and caffeine contractures: implications for malignant hyperthermia. *Acta Anaesthesiol Scand* 1989; **33**: 187–92

40 Fletcher JE, Rosenberg H, Aggarwal M. Comparison of European and North American malignant hyperthermia diagnostic protocol outcomes for use in genetic studies. *Anesthesiology* 1999; **90**: 654–61

41 Fu ES, Scharf JE, Mangar D, Miller WD. Malignant hyperthermia involving the administration of desflurane. *Can J Anaesth* 1996; **43**: 687–90

42 Fujii J, Otsu K, Zorzato F *et al*. Identification of a mutation in porcine ryanodine receptor associated with malignant hyperthermia. *Science* 1991; **253**: 448–51

43 Gillard EF, Otsu K, Fujii J *et al*. A substitution of cysteine for arginine 614 in the ryanodine receptor is potentially causative of human malignant hyperthermia. *Genomics* 1991; **11**: 751–5

44 Gilly H, Musat I, Fricker R, Bittner RE, Steinbereithner K, Kress HG. Classification of malignant hyperthermia-equivocal patients by 4-chloro-*m*-cresol. *Anesth Analg* 1997; **85**: 149–54

45 Gronert GA, Antognini JF. Clinical management of malignant hyperthermia. In: Hopkins PM, Ellis FR, eds. *Hyperthermic and Hypermetabolic Disorders*. Cambridge: Cambridge University Press, 1996; 119–31

46 Gronert GA, White DA. Failure of norepinephrine to initiate porcine malignant hyperthermia. *Pflugers Arch* 1988; **411**: 226–8

47 Gronert GA, Milde JH, Theye RA. Role of sympathetic activity in porcine malignant hyperthermia. *Anesthesiology* 1977; **47**: 411–5

48 Haberman ML. Malignant hyperthermia. An allergic reaction to thioridazine therapy. *Arch Int Med* 1978; **138**: 800–1

49 Hackl W, Mauritz W, Schemper M, Winkler M, Sporn P, Steinbereithner K. Prediction of malignant hyperthermia susceptibility: statistical evaluation of clinical signs. *Br J Anaesth* 1990; **64**: 425–9

50 Hackl W, Winkler M, Mauritz W, Sporn P, Steinbereithner K. Muscle biopsy for diagnosis of malignant hyperthermia susceptibility in two patients with severe exercise-induced myolysis. *Br J Anaesth* 1991; **66**: 138–40

51 Hall GM, Lister D. Procaine and malignant hyperthermia *Lancet* 1974; **i**: 208

52 Halsall PJ. Clinical presentation of malignant hyperthermia In: Hopkins PM, Ellis FR, eds. *Hyperthermic and Hypermetabolic Disorders*. Cambridge: Cambridge University Press, 1996; 107–18

53 Halsall PJ, Ellis FR Does postoperative pyrexia indicate malignant hyperthermia susceptibility? *Br J Anaesth* 1992; **68**: 209–10

54 Halsall PJ, Bridges LR, Ellis FR, Hopkins PM. Should patients with central core disease be screened for malignant hyperthermia? *J Neurol Neurosurg Psychiatry* 1996; **61**. 119–21

55 Harrison GG, Isaacs H. Malignant hyperthermia. An historical vignette. *Anaesthesia* 1992; **47**: 54–6

56 Hartung E, Koob M, Anetseder M *et al*. Malignant hyperthermia (MH) diagnostics: a comparison between the halothane–caffeine- and the ryanodine-contracture-test results in MH susceptible, normal and control muscle. *Acta Anaesthesiol Scand* 1996; **40**: 437–44

57 Healy SJ, Heffron JJ, Lehane M, Bradley DG, Johnson K, McCarthy TV. Diagnosis of susceptibility to malignant hyperthermia with flanking DNA markers. *BMJ* 1991; **303**: 1225–8

58 Heffron JJ, Mitchell G. Procaine for malignant hyperthermia. *New Engl J Med* 1975; **292**: 266–7

59 Hopkins PM. The effect of suxamethonium on intracellular calcium ion concentration of isolated rat skeletal muscle. *Br J Anaesth* 1994; **73**: 717P

60 Hopkins PM. Masseter muscle spasm. In: Goldstone JC, Pollard BJ, eds. *Handbook of Clinical Anaesthesia*. London: Churchill Livingstone, 1996; 646–7

61 Hopkins PM, Ellis FR. Inherited disease affecting anaesthesia. In: Healy TEJ, Cohen PJ, eds. *A Practice of Anaesthesia*, 6th edn London: Edward Arnold, 1995, 938–52

62 Hopkins PM, Ellis FR, Halsall PJ. Evidence for related myopathies in exertional heat stroke and malignant hyperthermia. *Lancet* 1991; **338**: 1491–2

63 Hopkins PM, Ellis FR, Halsall PJ. Ryanodine contracture: a potentially specific in vitro diagnostic test for malignant hyperthermia. *Br J Anaesth* 1991; **66**: 611–3

64 Hopkins PM, Ellis FR, Halsall PJ. Comparison of *in vitro* contracture testing with ryanodine, halothane and caffeine in malignant hyperthermia and other neuromuscular disorders. *Br J Anaesth* 1993; **70**: 397–401

65 Hopkins PM, Halsall PJ, Ellis FR. Diagnosing malignant hyperthermia susceptibility *Anaesthesia* 1994; **49** 373–5

66 Hopkins PM, Ellis FR, Halsall PJ, Stewart AD. An analysis of the predictive probability of the *in vitro* contracture test for determining susceptibility to malignant hyperthermia. *Anesth Analg* 1997; **84**: 648–56

67 Hopkins PM, Hartung E, Wappler F, The European Malignant Hyperthermia Group Multicentre evaluation of ryanodine contracture testing in malignant hyperthermia. *Br J Anaesth* 1998; **80**: 389–94

68 Iles DE, Segers B, Sengers RC *et al.* Genetic mapping of the beta 1- and gamma-subunits of the human skeletal muscle L-type voltage-dependent calcium channel on chromosome 17q and exclusion as candidate genes for malignant hyperthermia susceptibility. *Hum Mol Genet* 1993; **2**: 863–8

69 Iles DE, Lehmann-Horn F, Scherer SW *et al.* Localization of the gene encoding the alpha 2/delta-subunits of the L-type voltage-dependent calcium channel to chromosome 7q and analysis of the segregation of flanking markers in malignant hyperthermia susceptible families. *Hum Mol Genet* 1994; **3**: 969–75

70 Isaacs H, Badenhorst M. False-negative results with muscle caffeine halothane contracture testing for malignant hyperthermia. *Anesthesiology* 1993; **79**. 5–9

71 Islander G, Henriksson KG, Ranklev-Twetman E. Malignant hyperthermia susceptibility without central core disease (CCD) in a family where CCD is diagnosed *Neuromusc Disord* 1995; **5**: 125–7

72 Johnson K. Malignant hyperthermia hots up. *Hum Mol Genet* 1993; **2**. 849

73 Kawana Y, Iino M, Horiuti K *et al.* Acceleration in calcium-induced calcium release in the biopsied muscle fibers from patients with malignant hyperthermia *Biomed Res* 1992; **13**: 287–97

74 Keating KE, Giblin L, Lynch PJ *et al.* Detection of a novel mutation in the ryanodine receptor gene in an Irish malignant hyperthermia pedigree: correlation of the IVCT response with the affected and unaffected haplotypes. *J Med Genet* 1997; **34**: 291–6

75 Larach MG. Standardization of the caffeine halothane muscle contracture test. North American Malignant Hyperthermia Group. *Anesth Analg* 1989; **69**: 511–5

76 Larach MG, Rosenberg H, Larach DR, Broennle AM. Prediction of malignant hyperthermia susceptibility by clinical signs. *Anesthesiology* 1987; **66**: 547–50

77 Larach MG, Landis JR, Bunn JS, Diaz M. Prediction of malignant hyperthermia susceptibility in low-risk subjects. An epidemiologic investigation of caffeine halothane contracture responses. The North American Malignant Hyperthermia Registry. *Anesthesiology* 1992; **76**: 16–27

78 Larach MG, Localio AR, Allen GC *et al.* A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology* 1994; **80**: 771–9

79 Laurence AS Serum myoglobin and creatine kinase following surgery. *Br J Anaesth* 2000; **85**: 763–6.

80 Laurence AS, Vanner GK, Collins W, Hopkins PM Serum and urinary myoglobin following an aborted malignant hyperthermia reaction. *Anaesthesia* 1996; **51** 958–61

81 Leary NP, Ellis FR. Masseteric muscle spasm as a normal response to suxamethonium. *Br J Anaesth* 1990, **64**: 488–92

82 Lenzen C, Roewer N, Wappler F *et al.* Accelerated contractures after administration of ryanodine to skeletal muscle of malignant hyperthermia susceptible patients. *Br J Anaesth* 1993, **71**: 242–6

83 Levitt RC, Nouri N, Jedlicka AE *et al.* Evidence for genetic heterogeneity in malignant hyperthermia susceptibility. *Genomics* 1991; **11**: 543–7

84 Levitt RC, Olckers A, Meyers S *et al.* Evidence for the localization of a malignant hyperthermia susceptibility locus (*MHS2*) to human chromosome 17q. *Genomics* 1992; **14**: 562–6

85 Lister D, Hall GM, Lucke JN. Porcine malignant hyperthermia III: Adrenergic blockade. *Br J Anaesth* 1976; **48**: 831–8

86 Littleford JA, Patel LR, Bose D, Cameron CB, McKillop C. Masseter muscle spasm in children: implications of continuing the triggering anesthetic. *Anesth Analg* 1991; **72**. 151–60

87 Lopez JR, Allen PD, Alamo L, Jones D, Sreter FA. Myoplasmic free [Ca^{2+}] during a malignant hyperthermia episode in swine. *Muscle Nerve* 1988; **11**: 82–8

88 Lucke JN, Denny H, Hall GM, Lovell R, Lister D. Porcine malignant hyperthermia VI. The effects of bilateral adrenalectomy and pretreatment with bretylium on the halothane-induced response. *Br J Anaesth* 1978, **50**. 241–6

89 MacKenzie AE, Korneluk RG, Zorzato F *et al* The human ryanodine receptor gene: its mapping to 19q13.1, placement in a chromosome 19 linkage group, and exclusion as the gene causing myotonic dystrophy *Am J Hum Genet* 1990, **46**: 1082–9

90 MacLennan DH, Duff C, Zorzato F *et al.* Ryanodine receptor gene is a candidate for predisposition to malignant hyperthermia. *Nature* 1990; **343**: 559–61

91 Madson L, Raab CR, Kahl SD *et al.* Identification and characterization of the high affinity [^3H]ryanodine receptor of the junctional sarcoplasmic reticulum Ca^{2+} release channel. *J Biol Chem* 1987; **262** 6460–3

92 Manning BM, Quane KA, Lynch PJ *et al* Novel mutations at a CpG dinucleotide in the ryanodine receptor in malignant hyperthermia. *Hum Mutat* 1998; **11** 45–50

93 Manning BM, Quane KA, Ording H *et al.* Identification of novel mutations in the ryanodine-receptor gene (*RYR1*) in malignant hyperthermia: genotype–phenotype correlation *Am J Hum Genet* 1998; **62**: 599–609

94 Marwaha J Some mechanisms underlying actions of ketamine on electromechanical coupling in skeletal muscle. *J Neurosci Res* 1980; **5**: 43–50

95 McCarthy TV, Healy JM, Heffron JJ *et al.* Localization of the malignant hyperthermia susceptibility locus to human chromosome 19q12-13.2. *Nature* 1990; **343**: 562–4

96 Michalek-Sauberer A, Fricker R, Gradwohl I, Gilly H. A case of suspected malignant hyperthermia during desflurane administration. *Anesth Analg* 1997, **85**: 461–2

97 Mickelson JR, Gallant EM, Litterer LA, Johnson KM, Rempel WE, Louis CF. Abnormal sarcoplasmic reticulum ryanodine receptor in malignant hyperthermia. *J Biol Chem* 1988; **263**. 9310–5

98 Mitchell G, Heffron JJ. Procaine in porcine malignant hyperthermia. *Br J Anaesth* 1975; **47** 667–8

99 Monnier N, Procaccio V, Stieglitz P, Lunardi J. Malignant-hyperthermia susceptibility is associated with a mutation of the alpha 1-subunit of the human dihydropyridine-sensitive L-type voltage-dependent calcium-channel receptor in skeletal muscle. *Am J Hum Genet* 1997; **60** 1316–25

100 Moyes DG. Malignant hyperpyrexia caused by trimeprazine. *Br J Anaesth* 1973; **45**: 1163–4

101 Mullis KB, Faloona FA. Specific synthesis of DNA in vitro via a polymerase catalyzed chain reaction. *Methods Enzymol* 1987; **155**: 335–50

102 Ording H, Nielsen VG. Atracurium and its antagonism by neostigmine (plus glycopyrrolate) in patients susceptible to malignant hyperthermia. *Br J Anaesth* 1986; **58**: 1001–4

103 Ording H, Brancadoro V, Cozzolino S *et al* In vitro contracture test for diagnosis of malignant hyperthermia following the protocol of the European MH Group: results of testing patients surviving fulminant MH and unrelated low-risk subjects. The European Malignant Hyperthermia Group. *Acta Anaesthesiol Scand* 1997; **41**: 955–66

104 Ording H, Glahn K, Gardi T, Fagerlund T, Bendixen D. 4-Chloro-*m*-cresol test—a possible supplementary test for diagnosis of malignant hyperthermia susceptibility. *Acta Anaesthesiol Scand* 1997; **41**: 967–72

105 Otsuka H, Kemmotsu O. Malignant hyperthermia during sevoflurane anesthesia. *Anesth Analg* 1992; **75**: 867

106 Phillips MS, Khanna VK, de Leon S, Frodis W, Britt BA, MacLennan DH. The substitution of Arg for Gly2433 in the human skeletal muscle ryanodine receptor is associated with malignant hyperthermia. *Hum Mol Genet* 1994; **3**: 2181–6

107 Quane KA, Keating KE, Healy JM *et al*. Mutation screening of the *RYR1* gene in malignant hyperthermia: detection of a novel Tyr to Ser mutation in a pedigree with associated central cores. *Genomics* 1994; **23**: 236–9

108 Quane KA, Ording H, Keating KE *et al*. Detection of a novel mutation at amino acid position 614 in the ryanodine receptor in malignant hyperthermia. *Br J Anaesth* 1997; **79**: 332–7

109 Ramirez JA, Cheetham ED, Laurence AS, Hopkins PM. Suxamethonium, masseter spasm and later malignant hyperthermia. *Anaesthesia* 1998; **53**: 1111–6

110 Robinson RL, Monnier N, Wolz W *et al*. A genome wide search for susceptibility loci in three European malignant hyperthermia pedigrees. *Hum Mol Genet* 1997; **6**: 953–61

111 Robinson R, Curran JL, Hall WJ *et al*. Genetic heterogeneity and HOMOG analysis in British malignant hyperthermia families. *J Med Genet* 1998; **35**: 196–201

112 Ruff RL. Calcium sensitivity of fast- and slow-twitch human muscle fibers *Muscle Nerve* 1989; **12**: 32–7

113 Ryan JF, Lopez JR, Sanchez VB, Sreter FA, Allen PD. Myoplasmic calcium changes precede metabolic and clinical signs of porcine malignant hyperthermia. *Anesth Analg* 1994; **79**: 1007–11

114 Scholes NW, Jenden DJ, Creese R, Blumm JJ. The mechanism of action of ryanodine on skeletal muscle. *J Pharmacol Exp Ther* 1957; **121**: 477–52

115 Strazis KP, Fox AW. Malignant hyperthermia: a review of published cases. *Anesth Analg* 1993; **77**: 297–304

116 Sudbrak R, Golla A, Hogan K *et al*. Exclusion of malignant hyperthermia susceptibility (MHS) from a putative *MHS2* locus on chromosome 17q and of the alpha 1, beta 1, and gamma subunits of the dihydropyridine receptor calcium channel as candidates for the molecular defect. *Hum Mol Genet* 1993; **2**: 857–62

117 Sudbrak R, Procaccio V, Klausnitzer M *et al*. Mapping of a further malignant hyperthermia susceptibility locus to chromosome 3q13.1. *Am J Hum Genet* 1995; **56**: 684–91

118 Sudo RT, Nelson TE. Changes in ryanodine-induced contractures by stimulus frequency in malignant hyperthermia susceptible and malignant hyperthermia nonsusceptible dog skeletal muscle. *J Pharmacol Exp Ther* 1997; **282**: 1331–6

119 Tegazzin V, Scutari E, Treves S, Zorzato F. Chlorocresol, an additive to commercial succinylcholine, induces contracture of human malignant hyperthermia-susceptible muscles via activation of the ryanodine receptor Ca^{2+} channel. *Anesthesiology* 1996; **84**: 1380–5

120 Tong J, Oyamada H, Demaurex N, Grinstein S, McCarthy TV, MacLennan DH. Caffeine and halothane sensitivity of intracellular Ca^{2+} release is altered by 15 calcium release channel (ryanodine receptor) mutations associated with malignant hyperthermia and/or central core disease. *J Biol Chem* 1997; **272**: 26332–9

121 Tong J, McCarthy TV, MacLennan DH. Measurement of resting cytosolic Ca^{2+} concentrations and Ca^{2+} store size in HEK-293 cells transfected with malignant hyperthermia or central core disease mutant Ca^{2+} release channels. *J Biol Chem* 1999; **274**: 693–702

122 van der Spek AF. Triggering agents continued after masseter spasm: there is proof in this pudding. *Anesth Analg* 1991; **73**: 364–5

123 van der Spek AF, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA. The effects of succinylcholine on mouth opening. *Anesthesiology* 1987; **67**: 459–65

124 Wappler F, Roewer N, Lenzen C *et al*. High-purity ryanodine and 9,21-dehydroryanodine for *in vitro* diagnosis of malignant hyperthermia in man. *Br J Anaesth* 1994; **72**: 240–2

125 Wappler F, Roewer N, Kochling A, Scholz J, Steinfath M, Schulte am Esch J. *In vitro* diagnosis of malignant hyperthermia susceptibility with ryanodine-induced contractures in human skeletal muscles. *Anesth Analg* 1996; **82**: 1230–6

126 Wappler F, Scholz J, von Richthofen V, Fiege M, Steinfath M, Schulte am Esch J. [4-Chloro-*m*-cresol-induced contractures of skeletal muscle specimen from patients at risk for malignant hyperthermia]. [German]. *Anasthesiol Intensivmed Notfallmed Schmerzther* 1997; **32**: 541–8

127 Wingard DW, Bobko S. Failure of lidocaine to trigger porcine malignant hyperthermia. *Anesth Analg* 1979; **58**: 99–103

128 Xu L, Jones R, Meissner G. Effects of local anesthetics on single channel behavior of skeletal muscle calcium release channel. *J Gen Physiol* 1993; **101**: 207–33

129 Yamazawa T, Takeshima H, Sakurai T, Endo M, Iino M. Subtype specificity of the ryanodine receptor for Ca^{2+} signal amplification in excitation–contraction coupling. *EMBO J* 1996; **15**: 6172–7

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Neuroleptic malignant syndrome

P. Adnet*, P. Lestavel and R. Krivosic-Horber

Department of Anesthesiology and Emergency Medicine, University Hospital, Lille, France
**Corresponding author: Professor P. Adnet, Service d'acceuil et d'urgence, hôpital R. Salengro, CHU de Lille, F-59037 Lille, France*

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Neuroleptic malignant syndrome (NMS) is a relatively rare but potentially fatal complication of the use of neuroleptic drugs. It was first described by Delay and colleagues after the introduction of neuroleptics in 1960; they called it 'akinetic hypertonic syndrome'.[16] Over the last decade, almost 1000 cases of NMS have been reported, but many features of this syndrome remain controversial. Indeed, a graded scale of specific signs and symptoms for the diagnosis of NMS and a spectrum of clinical severity are two issues that await resolution.[1 22] Many diagnostic criteria have been proposed, but no single set of criteria has been adopted for general use. Different presentations of this disorder could explain some of the contradictory findings associated with NMS; these include the following: (i) prospective studies have provided disparate estimates of the frequency of NMS, ranging from 0.07%[20] to 2.2%[26] among patients receiving neuroleptic agents; (ii) risk factors for NMS vary in different patient populations;[29] and (iii) the association between NMS and other potentially fatal syndromes, such as malignant hyperthermia, is unclear.

Pathogenesis of NMS

Two major, though not necessarily competing, theories to explain NMS are a neuroleptic-induced alteration of central neuroregulatory mechanisms and an abnormal reaction of predisposed skeletal muscle. This latter hypothesis is based on similarities between NMS and malignant hyperthermia and suggests that neuroleptic medications induce abnormal calcium availability in muscle cells of susceptible individuals and trigger muscle rigidity, rhabdomyolysis and hyperthermia. Alternatively, in some circumstances, it is possible that neuroleptics could be directly toxic to normal skeletal muscle.

Central dopamine receptor blockade

Dopamine plays a role in central thermoregulation in mammals. A dopamine injection into the preoptic–anterior hypothalamus causes a reduction in core temperature.[14] Since neuroleptic drugs block dopamine receptor sites, the hyperthermia associated with NMS may result from a blockade of hypothalamic dopamine sites. This was suggested 20 yr ago by Henderson and Wooten, who reported a patient with Parkinson's disease and chronic psychosis who developed NMS when dopaminergic agonists were withdrawn but haloperidol was continued.[24] NMS has also been observed in a patient with Huntington's chorea taking methyltyrosine, a cathecholamine synthesis inhibitor, and tetrabenazine, which depletes central nervous system catecholamines.[10] This suggests that NMS is caused by dopamine depletion or blockade, leading to abnormal central thermoregulation. The dopamine blockade theory is supported by the report of a case in which NMS developed when L-dopa/carbidopa and amantadine were abruptly discontinued in a patient with Parkinson's disease who had never taken neuroleptics.[50] Some dopamine-function-enhancing drugs, such as bromocriptine[9] or amantadine,[36] have shown efficacy in treating NMS.

The blockade of dopamine receptors in the hypothalamus is thought to lead to impaired heat dissipation. In addition, blockade of dopamine receptors in the corpus striatum is thought to cause muscular rigidity, generating heat. The excess heat production, in association with a decrease in heat dissipation, produces hyperthermia, which is one of the main signs of the syndrome. The peripheral anticholinergic effects of neuroleptics which reduce sweating probably do not play a major role in hyperthermia associated with NMS since most NMS patients (70%) are in a sweat. However, it is unlikely that blockade of dopamine receptors in the hypothalamus and corpus striatum could completely explain all the signs of NMS. Indeed, hypothalamic thermoregulation involves noradrenergic, serotoninergic, cholinergic and central dopaminergic pathways[7] Many neuroleptics may have additional selective effects on peptides co-transmitting with dopamine in the striatum and other parts of the brain.

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Primary skeletal muscle defect similar to malignant hyperthermia

A common pathophysiology of NMS and malignant hyperthermia has been suggested.[15 17 49] This hypothesis is based mainly on three points: (i) NMS and malignant hyperthermia have clinical features in common, including hyperthermia, rigidity, an elevated creatine kinase concentration and a mortality rate for both NMS and malignant hyperthermia of 10–30%; (ii) sodium dantrolene, a peripheral muscle relaxant, has been used successfully in both syndromes; (iii) abnormal results have been found in *in vitro* contractility tests in patients with NMS or malignant hyperthermia. These *in vitro* halothane–caffeine tests are at present the most reliable diagnostic measure for patients susceptible to malignant hyperthermia.[47] They determine the sensitivity of muscle fibres to halothane or caffeine added to the bathing solution. Muscle fibres from patients susceptible to malignant hyperthermia contract in response to these drugs at a lower concentration than those from normal patients. Hence, in order to evaluate a possible association between NMS and malignant hyperthermia, several investigators have used such tests on skeletal muscle fibres removed from patients with documented NMS episodes. However, conflicting results have been reported regarding the prevalence of malignant hyperthermia susceptibility among NMS patients.[2 5 13] Three main series and some sporadic case reports have been published. Caroff and colleagues[13] found that five of seven NMS patients were susceptible to malignant hyperthermia on the basis of a 3% halothane response. Araki and colleagues[5] showed, using a caffeine skinned fibre technique, that there was abnormal contracture in six NMS patients similar to that seen in malignant hyperthermia. Our laboratory[2 32] found that 13 of 14 NMS patients were not susceptible to malignant hyperthermia and the other was equivocal.

One possible explanation for these discrepancies is that patients diagnosed as having NMS may be a heterogeneous group with great variability in clinical presentation, response to treatment and, possibly, response to test drugs. Some of the variation in the *in vitro* results from different centres may be attributable to variations in laboratory procedures. The variety of tests used for diagnosing malignant hyperthermia diagnosis included using caffeine alone,[5] halothane and caffeine on separate muscle bundles,[32] halothane with cumulative concentrations of caffeine,[49] or caffeine on skinned muscle fibres.[5] The sensitivity of this latter method may be inadequate as the technique itself excludes any detection of a possible defect in the sarcolemma.[4] Differences were also observed in the criteria used for diagnosing malignant hyperthermia based on *in vitro* contracture tests:[13] some centres used the development of a contracture of >0.5 g force in response to 1% halothane as a threshold while others chose >0.7 g force in response to 3% halothane. The European malignant hyperthermia group[17] required, for an abnormal response to halothane, a contracture of ⩾0.2 g force in response to <2% halothane. In other sporadic case reports, the protocol and diagnostic criteria were not fully explained.

The time interval between adverse reaction to the neuroleptic drug and the biopsy was either not specified,[5] or was 1 month[13] or 2–3 weeks.[2 32] Caroff and colleagues[13] found no correlation between the maximum halothane response and the time between normalization of creatine kinase concentration and biopsy. However, contracture test results in NMS patients may be falsely positive and reflect coincidental changes in muscle resulting from NMS. For example, Gallant and colleagues[19] reported that muscle fibre injury during biopsy and *in vitro* testing procedures enhances halothane sensitivity and could contribute to false-positive contracture test results. Denborough, Collins and Hopkinson[17] reported positive results in two patients who recovered from non-drug-related episodes of rhabdomyolysis. Adnet and colleagues[3] found that if cut fibre specimens depolarize with time after biopsy, these preparations become less sensitive to caffeine, and so one must be cautious when interpreting the results of *in vitro* caffeine contracture test. This suggests that non-specific muscle damage secondary to metabolic factors, drug exposure, abnormalities in central nervous system activity or testing procedures may have contributed to the abnormal responses observed *in vitro* in muscle obtained from survivors of NMS episodes. Since our previous reports, 19 additional patients have been investigated according to the European malignant hyperthermia protocol. None of these patients were susceptible to malignant hyperthermia and two patients were equivocal. Statistical analysis for inferences based upon negative results can be performed. The increase in our study group size from 14 to 33 patients decreases the likelihood of malignant hyperthermia occurring in NMS patients from 31% to <10% with 95% confidence. Our study does not justify abandoning precautions against malignant hyperthermia in NMS patients. Mathematical analysis suggests that 59 consecutive NMS patients would have to test negative, with a similar *in vitro* protocol, in order to exclude statistically any cross-reactivity between malignant hyperthermia and NMS. Until such results are available, we suggest that all patients with clinical NMS should be tested for susceptibility to malignant hyperthermia before being considered at risk of this disorder during anaesthesia.

Direct toxic effect on skeletal muscle induced by neuroleptics

Muscle contracture has been induced *in vitro* by neuroleptic agents such as chlorpromazine.[31] The drug is reported to influence calcium ion transport across the sarcoplasmic reticulum, and has been studied in various experimental muscle preparations. In a study on skinned fibres, chlorpromazine influenced both the contractile system and the function of the sarcoplasmic reticulum.[45] However, it has been shown previously that the drug induced contracture to the same extent in both NMS and normal muscle.[2] Likewise, Caroff and colleagues[13] also found no significant differences in the muscle response to another neuroleptic drug, fluphenazine, between NMS, malignant hyperthermia-susceptible and control patients.

To explore further a possible direct action of neuroleptic drugs on skeletal muscle, we analysed the *in vitro* muscle contracture response to four neuroleptic agents implicated in NMS episodes.[40] Muscle from NMS patients was no more sensitive to neuroleptic drugs than muscle from normal patients. These negative findings may indicate that the *in vitro* contracture response to neuroleptic agents does not correlate with clinical evidence of NMS. However, this may also show that neuroleptics are potentially active on skeletal muscle. Thus, it is possible that, in some circumstances, such as exhaustion, psychomotor agitation or dehydration, which are not explored by the *in vitro* method, neuroleptics may be toxic to skeletal muscle, leading to contracture and rhabdomyolysis. Therefore, neuroleptic contracture tests may not adequately reproduce conditions *in vivo*. Many factors present *in vivo*, such as neuroleptic metabolites, central dopaminergic blockade and risk factors for NMS, should be taken into consideration in developing more precise pharmacological models to explore possible interactions between neuroleptics and skeletal muscle function. Of particular interest is the fact that rechallenge with the original agent may not result in a recurrence of NMS. This suggests that neuroleptics may be a necessary, but not exclusive, cause of the syndrome.[12 34]

In vivo *experimental model for NMS*

Very recently, an experimental model for NMS has been developed. Rabbits treated with haloperidol and exposed to high ambient temperature may be useful in elucidating the pathogenesis of NMS.[46]

Molecular basis of NMS

The molecular basis for NMS is unclear, but studies suggest that genetic factors are involved in its pathogenesis.[27] Involvement of the serotonergic system in NMS has been suggested, but polymorphisms in the 5-HT1A and 5-HT2A receptor genes do not determine susceptibility to NMS.[28] Other studies do not support an association between NMS and the mutations in the ryanodine receptor gene reported with malignant hyperthermia.[38]

Clinical features

Table 1 Criteria for guidance in the diagnosis of neuroleptic malignant syndrome The presence of all three major, or two major and four minor, manifestations indicates a high probability of the presence of neuroleptic malignant syndrome, if supported by clinical history (e g not indicative of malignant hyperthermia) (from reference 34)

Category	**Manifestations**
Major	Fever, rigidity, elevated creatine phosphokinase concentration
Minor	Tachycardia, abnormal arterial pressure, tachypnoea, altered consciousness, diaphoresis, leucocytosis

NMS typically develops over a period of 24–72 h but many investigators have described a more insidious evolution of symptoms. The risk of developing NMS has been reported to last for 10–20 days after oral neuroleptics are discontinued and even longer when associated with depot forms of the drugs. Consistent diagnostic criteria have been used only in some clinical studies.[29–31] Three major symptoms indicate a high probability of the presence of NMS. hyperthermia, rigidity and an elevated creatine phosphokinase concentration, reflecting rhabdomyolysis[34] (Table 1). In the absence of these criteria, the diagnosis of NMS should be questioned, since other symptoms of the disorder may be seen in patients taking neuroleptics without having NMS. Elevated temperature (≥38.5°C) in the absence of other systemic illness is observed in most patients. Muscle rigidity consists of a generalized 'lead pipe' increase in tone which may result in decreased chest-wall compliance with resulting tachypnoeic hypoventilation and pulmonary infection secondarily. This increase in muscle tone may be accompanied by extrapyramidal symptoms including dyskinesia, dysarthria or Parkinsonism. The creatine phosphokinase concentration is always elevated (>1000 IU litre^{-1}), reflecting myonecrosis secondary to intense muscle contracture. This often results in acute myoglobinuric renal failure. Minor signs alone do not indicate a high probability of NMS. Diaphoresis, tachycardia and abnormally high arterial pressure are common signs of autonomic dysfunction. Altered consciousness ranges from agitation to stupor or coma. Many other clinical signs of lesser frequency have been reported, including opisthotonos, grand mal seizures, Babinski's signs, chorea and trismus.

Leucocytosis, ranging from a slight elevation to 30 000 mm^{-3}, is the only frequent laboratory finding included in the minor signs of NMS. Other non-specific laboratory abnormalities have been reported, such as mildly elevated hepatic enzymes (transaminase, lactic dehydrogenase and alkaline phosphatase). Non-specific encephalopathy may occur. Lumbar puncture should be done for the differential diagnosis but is usually normal in NMS. Cerebral CT scan is normal; non-specific changes are usually observed in muscle biopsy or post-mortem histopathological studies of the brain.

Some authors are in favour of an approach whereby a diagnosis of NMS is only made if certain signs are present. For example, Levenson[34] suggests that the presence of all three major, or two major and four minor signs (Table 1) indicates a high probability of NMS. These criteria for guidance in the diagnosis of NMS are commonly used in clinical research studies.[2] [13] Similarly, Pope, Keck and

McElroy[39] have published 'definite' and 'probable' criteria for NMS. Others still prefer to think in terms of a spectrum of neuroleptic-related neurotoxicity, with varying combinations that enhance the potential for inappropriate diagnosis or management.[35]

A decrease in mortality from NMS has been reported in recent years. NMS resulted in a 76% mortality before 1970, a 22% mortality from 1970 to 1980, and a 15% mortality since 1980. Shalev, Hermesh and Munitz[44] reported a significant decrease in mortality since 1984 (to 11%), which occurred independently of the treatment used: dopamine agonist or dantrolene. Renal failure is a strong predictor of mortality, representing a mortality risk of approximately 50%.

Medications and risk factors

A wide variety of antipsychotic agents is associated with this syndrome, including phenothiazines, butyrophenones, thioxanthenes, benzamides and miscellaneous novel antipsychotic agents such as clozapine and risperidone.[23] Other circumstances, such as abrupt discontinuation of neuroleptic or antiparkinsonian agents, and the use of dopamine-depleting agents, have also been reported to produce NMS. The onset of the syndrome is not related to the duration of exposure to neuroleptics or to toxic overdose. All ages (including children) and both genders are affected in NMS but young adult males predominate among reported cases. Cases have been reported in both psychiatric and medical patients including after multiple trauma or preoperative use of neuroleptic agents. Alcoholic patients are at greater risk of developing NMS during treatment of delirium or its prevention by droperidol or tiapride.[2] Abnormalities of muscle metabolism in alcoholic patients are caused by ethanol toxicity and malnutrition.[8] This may sensitize the muscle to the action of neuroleptics. In a psychiatric population, several studies[6 30 42] showed that patients with NMS displayed significantly greater psychomotor agitation, received significantly higher doses of neuroleptics at greater dose increments, and received more intramuscular injections than other patients having similar medication without evidence of NMS. Many authors have pointed out that most cases have occurred in patients receiving haloperidol or, to a lesser extent, depot fluphenazine. These clinical observations do not necessarily mean that the two drugs carry a higher risk of causing NMS. One must consider the frequency with which the drug is prescribed: haloperidol is one of the most commonly used medications. Furthermore, sicker patients are more likely to receive haloperidol or fluphenazine than other neuroleptics. Sicker patients may also be at higher risk of NMS because of greater likelihood of dehydration, exhaustion or malnutrition.[11 12 34] Other suggested predisposing factors include infection, concurrent organic brain disease or sympathoadrenal hyperactivity.[21]

Differential diagnosis

Patients on neuroleptics who develop hyperthermia, muscle rigidity and autonomic dysfunction should have all psychotropic medications withdrawn immediately until rigorous diagnostic investigation reveals a specific aetiology. Disorders that can be mistaken for NMS include rhabdomyolysis from other causes, central nervous system infections, a cerebral mass, tetanus and lithium toxicity. Other specific illnesses should be considered in the differential diagnosis of NMS, including neuroleptic-related heat stroke, catatonia, drug interactions with monoamine oxidase inhibitors, the central anticholinergic syndrome and anaesthetic-induced malignant hyperthermia. In order to make a diagnosis, the physician who is evaluating a patient with suspected NMS should carry out the following tests in addition to a careful history and physical examination: creatine phosphokinase concentration; white blood cell count; renal function; EEG; CT scan; lumbar puncture; and serum lithium concentration.

Neuroleptic-induced heat stroke

Classic heat stroke is a life-threatening condition in which heat gain from metabolism and the environment exceeds heat loss by evaporation and convection. Neuroleptics predispose to hyperthermia by their anticholinergic properties, which block sweating and heat dissipation, and by their antidopaminergic properties, which interfere with hypothalamic thermoregulation. Contributing factors include hot, humid weather and excessive agitation or exercise not accompanied by adequate fluid intake. When an acutely catastrophic disorder associated with hyperthermia and altered consciousness develops in a patient taking neuroleptics, early differential diagnosis between NMS and neuroleptic-induced heat stroke is imperative if potentially life-saving treatment, which differs according to the condition, is to be given promptly. Neuroleptic-induced heat stroke can be differentiated from NMS by abrupt onset, often with seizures, the absence of extrapyramidal signs, absence of sweating, and a history of physical exercise or exposure to high ambient temperature.[33] Heat stroke needs rapid, effective cooling methods initiated as early as possible with continuous monitoring of the core temperature and vigorous fluid replacement for both rehydration and a more rapid reduction in temperature.

Acute lethal catatonia

Lethal catatonia is a very rare psychiatric syndrome that shares some features with NMS, including hyperthermia, akinesia and muscle rigidity. Catatonic states as a result of severe akinesia are most common in patients on neuroleptics. Since laboratory findings, CT scans, EEGs and other somatic data have not yet been of value in differentiating the two conditions, the diagnosis requires careful detailing of the patient's condition in the preceding 2–3 weeks.[18] The catatonic syndrome may be preceded by emotional withdrawal, depressive symptoms, neglect of previous hobbies, anxiety symptoms or acute agitation. These signs do not differ from those of other patients with schizophrenia but they seldom last for >2 weeks. The complete picture is more likely to involve choreiform sterotypy, primitive hyperkinesias, torsion spasms and rhythmic circling movements of the arms. Death may result from respiratory arrest or cardiovascular collapse.

Drug interactions with monoamine oxidase inhibitors

Agitation, delirium, hyperthermic reactions and death have been described as adverse effects of monoamine oxidase inhibitors in combination with narcotic drugs or tricyclic antidepressants. It has been suggested that the amine reuptake inhibitory properties of tricyclic antidepressants could interact dangerously with the sympathomimetic properties of monoamine oxidase inhibitors. Similar signs may be seen with overdosage of monoamine oxidase inhibitors. Patients taking neuroleptics may also be receiving treatment with monoamide oxidase inhibitors.

Central anticholinergic syndrome

Peripheral signs of atropine poisoning characterize the syndrome, including dry skin, dry mouth, dilated pupils and urinary retention. The patient is usually confused and disorientated (anticholinergic delirium) and the temperature is often elevated. Physostigmine may induce a resolution of symptoms that is not observed in NMS.

Treatment

Successful treatment of NMS depends on early clinical recognition and prompt withdrawal of the neuroleptic agents. Neuroleptics cannot be removed by dialysis, and blood concentrations decline only slowly. General symptomatic treatment, such as hydration, nutrition and reduction of fever, is essential. Secondary complications, such as hypoxia, acidosis and renal failure, must be treated aggressively. Low-dose heparin seems to be indicated to prevent venous thrombosis in an immobilized patient. Other dopamine antagonists, such as metoclopramide, should be avoided. In Caroff's review of 60 cases,[12] supportive therapy was the predominant treatment modality. The benefit of adding specific therapies to supportive measures is still debated. Insufficient data are available to evaluate the efficacy of specific treatments reported in the literature. Potential benefits from their use cannot, therefore, be excluded. Only one study evaluated treatment options for NMS.[41] In a series of 64 cases derived from an extensive review of the literature, 11 patients received only supportive therapy. The others received additional therapies including dantrolene (14 patients), bromocriptine (22 patients), benzodiazepine (one patient) and combinations of the above (nine patients). Efficacy was evaluated in each case by determining the delay in the clinical response and time to complete recovery. Therapy with bromocriptine (5 mg orally or nasogastrically four times daily) was effective after approximately 1 day. This was significantly more rapid than that achieved by supportive therapy alone. Complete resolution was achieved more quickly with bromocriptine (10 days) or dantrolene (9 days; 2–3 mg kg^{-1} day^{-1} i.v. without exceeding 10 mg kg^{-1} day^{-1}) than with supportive therapy (15 days).

The place of sodium dantrolene, the drug of choice for malignant hyperthermia, is less well defined in the treatment of NMS. Sodium dantrolene inhibits calcium release from the sarcoplasmic reticulum, decreasing available calcium for ongoing muscle contracture. The drug is a non-specific, directly acting muscle relaxant and a decrease in body temperature coincides with muscle relaxation. Oxygen consumption diminishes and heart rate and respiratory rate decrease correspondingly. It has been suggested that the initial dosage should be 2 mg kg^{-1} given intravenously.[15] This dose may be repeated every 10 min, up to a total dose of 10 mg kg^{-1} day^{-1}. The oral dosage has ranged from 50 to 200 mg day^{-1}. Hepatic toxicity may occur with doses of >10 mg kg^{-1} day^{-1}.

Bromocriptine mesylate, a dopamine agonist, is also used to treat NMS.[9] Bromocriptine doses have ranged from 2.5 to 10 mg four times a day. Hypotension is the most limiting side-effect. The drug seems to be well tolerated by psychotic patients even though it is a strong central dopamine agonist. Rigidity may begin to decrease during the first few hours followed by a decrease in temperature, along with normalization of arterial pressure. This effect on rigidity and tremor strengthens the hypothesis of a dopamine-receptor blockade in NMS. Bromocriptine and dantrolene have been used together without complications.[41]

Another dopamine agonist, amantadine hydrochloride, has been used successfully in some cases.[36] Levodopa, combined with the dopadecarboxylase inhibitor carbidopa, has also been reported to be effective in reversing hyperthermia.[24] Treatment may have to be continued for several days. Anticholinergic drugs, such as benzatropine, usually do not reduce the rigidity of NMS and do not affect hyperthermia. Benzodiazepine derivatives, which enhance GABA-ergic function, have caused transient decreases in symptoms. In every case, these drugs are recommended to control 'agitated' patients being treated for NMS. Carbamazepine has been used successfully in two patients: NMS completely resolved within 8 h.[48]

Electroconvulsive therapy (ECT) has improved some of the syndrome's components, notably fever, sweating and level of consciousness.[25]

Recurrence of neuroleptic malignant syndrome

Since many patients with NMS are schizophrenics, they require further neuroleptic treatment in the course of their illness, often very soon after the onset of NMS. Rechallenge with drugs of the same milligram potency as the original stimulus in six patients resulted in recurrent NMS in five of the six patients, with two deaths. Rechallenge with less potent antipsychotics, such as thioridazine, was safe in nine of 10 cases.[44] McCarthy[37] reported a fatal case of neuroleptic syndrome after a milder episode 3 months earlier. The safest approach for prevention of recurrence is a regimen where doses of a low-potency neuroleptic are increased very slowly. Substitute treatments, such as lithium carbonate or ECT, may offer a safe alternative to those patients who respond to these treatments. Prevention of NMS awaits better understanding of the underlying pathophysiology. Of prime importance seems to be the avoidance of marked dehydration in neuroleptic-treated patients; this may reduce the prevalence and morbidity of the syndrome.

Electroconvulsive therapy in patients with a history of NMS

Since a common pathophysiology has been suggested between NMS and malignant hyperthermia,[17 49] the possibility that patients with a history of NMS may be vulnerable to developing malignant hyperthermia is an important factor when considering general anaesthesia, especially succinylcholine administration immediately before electrical stimulation for ECT. To date, there is no report in the literature of malignant hyperthermia as a complication of ECT in NMS patients. One study[25] found that none of the patients who had NMS and underwent ECT, nor their relatives who had also undergone ECT, had any malignant hyperthermia-like symptoms or other secondary effects despite repeated use of succinylcholine in all cases. The authors reported a total of 147 i.v. administrations of succinylcholine in a dose range of 15–30 mg in 12 patients without any complication. These results are consistent with sporadic reports of the safe use of ECT for patients with NMS (see reference 25 for review).

ECT with the use of succinylcholine, which is an effective and rapid mode of treatment for cases of NMS unresponsive to supportive medical therapy, is not, therefore, contraindicated. However, until the association, between NMS and malignant hyperthermia is conclusively disproved, careful metabolic monitoring of general anaesthesia is necessary.

References

1 Adityanjee PA, Singh S, Singh G, Ong S. Spectrum concept of neuroleptic malignant syndrome. *Br J Psychiatr* 1988; **153**: 107–11

2 Adnet PJ, Krivosic-Horber RM, Adamantidis MM *et al.* The association between the neuroleptic malignant syndrome and malignant hyperthermia. *Acta Anaesthesiol Scand* 1989; **33**: 676–80

3 Adnet PJ, Krivosic-Horber RM, Adamantidis MM, Haudecoeur G, Reyford HG, Dupuis BA. Is resting membrane potential a possible indicator of viability of muscle bundles used in the in vitro caffeine contracture test? *Anesth Analg* 1991, **74**: 105–11

4 Adnet PJ, Krivosic-Horber RM, Adamantidis MM, Reyford H, Cordonnier C, Haudecoeur G. Effects of calcium-free solution, calcium antagonists, and the calcium agonist BAY K 8644 on mechanical responses of skeletal muscle from patients susceptible to malignant hyperthermia *Anesthesiology* 1991; **75**: 413–19

5 Araki M, Takagi A, Higuchi I, Sugita H. Neuroleptic malignant syndrome: caffeine contracture of single muscle fibers and muscle pathology *Neurology* 1988; **38**: 297–301

6 Berardi D, Amore M, Keck PE, Troia M, Dellatti M. Clinical and pharmacologic risk factors for neuroleptic malignant syndrome: a case-control study. *Biol Psychiatr* 1998; **44**: 748–54

7 Blingh J, Cottle WH, Maskrey M. Influence of ambient temperature on the thermoregulatory responses to 5 hydroxytryptamine. noradrenalin and acetylcholine injected into the lateral cerebral ventricles of sheep, goats and rabbits. *J Physiol* 1971; **212**: 377–92

8 Bollaert PE, Robin-Lherbier B, Escange JM *et al.* Phosphorus nuclear magnetic resonance: evidence of abnormal skeletal muscle metabolism in chronic alcoholics. *Neurology* 1989; **39**: 821–4

9 Bond WS. Detection and management of the neuroleptic malignant syndrome. *Clin Pharmacol* 1984; **3**: 302–7

10 Burke RE, Fahn S, Mayeux R. Neuroleptic malignant syndrome caused by dopamine depleting drugs in a patient with Huntington's chorea. *Neurology (NY)* 1981; **31**: 1022–6

11 Cao L, Katz RH. Acute hypernatremia and neuroleptic malignant syndrome in Parkinson disease. *Am J Med Sci* 1999; **318**: 67–8

12 Caroff SN. The neuroleptic malignant syndrome. *J Clin Psychiatr* 1980; **41**: 79–83

13 Caroff SN, Rosenberg H, Fletcher JE, Heiman-Patterson TD, Mann SC. Malignant hyperthermia susceptibility in neuroleptic malignant syndrome. *Anesthesiology* 1987; **67**: 20–5

14 Cox B, Kerwin R, Lee TE Dopamine receptors in the central thermoregulatory pathways of the rat. *J Physiol (Lond.)* 1978; **282**: 471–83

15 Delacour JL, Daoudal P, Chapoutot JL, Rocq B. Traitement du syndrome malin des neuroleptiques par le dantrolène. *Nouv Presse Méd* 1981; **10**: 3572–3

16 Delay J, Pichot P, Lempiere T, Blissalde B, Peigne F. Un neuroleptique majeur non phenothiazinique et non réserpinique, l'halopéridol, dans le traitement des psychoses. *Ann Med Psychol* 1960; **18**: 145–52

17 Denborough MA, Collins SP, Hopkinson KC. Rhabdomyolysis and malignant hyperpyrexia. *Br Med J* 1985; **ii**: 1878

18 Fleischbacker WW, Unterweger B, Kane JM, Hinterhuber H. The neuroleptic malignant syndrome and its differentiation from lethal catatonia *Acta Psychiatr Scand* 1990; **81**: 3–5

19 Gallant EM, Fletcher TF, Goettl VM, Rempel WE. Porcine malignant hyperthermia: cell injury enhances halothane sensitivity of biopsies. *Muscle Nerve* 1986; **9**: 174–84

20 Gelenberg AJ, Bellinghausen B, Wojcik JD, Falk WE, Sachs GS. Aprospective survey of neuroleptic malignant syndrome in a short-term psychiatric hospital. *Am J Psychiatr* 1988; **145**: 517–8

21 Gurrera RJ. Sympathoadrenal hyperactivity and the ethiology of neuroleptic malignant syndrome *Am J Psychiatr* 1999; **156**: 169–80

22 Guze BH, Baxter CR. Current concepts. Neuroleptic malignant syndrome. *New Engl J Med* 1985; **313**: 163–6

23 Hasan S, Buckley P. Novel antipsychotics and the neuroleptic malignant syndrome: a review and critique. *Am J Psychiatr* 1998; **155**: 1113–6

24 Henderson VW, Wooten GF. Neuroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockade? *Neurology* 1981, **31**: 132–7

25 Hermesh H, Aizenberg D, Weizman A. A successful electroconvulsive treatment of neuroleptic malignant syndrome. *Acta Psychiatr Scand* 1987; **75**: 237–9

26 Hermesh H, Aizenberg D, Lapidot M, Munitz H. Risk of malignant hyperthermia among patients with neuroleptic malignant syndrome and their families. *Am J Psychiatr* 1988; **145**: 1431–4

27 Kawanishi C, Hanihara T, Maruyama Y *et al.* Neuroleptic malignant syndrome and hydroxylase gene mutations: no association with CYP2D6A or CYP2D6B. *Psychiatr Gen* 1997; **7**: 127–9

28 Kawanishi C, Hanihara T, Shimoda Y *et al.* Lack of association between neuroleptic malignant syndrome and polymorphisms in the 5-HT1A and 5HT2A receptor genes *Am J Psychiatr* 1998; **155**: 1275–7

29 Keck PE, Pope H, Cohen BM, McElroy SL, Nierenberg AA. Risk factors for neuroleptic malignant syndrome. *Arch Gen Psychiatr* 1989; **46**: 914–8

30 Keck PE, Harrisson G, Pope JR, McElroy SL. Declining frequency of neuroleptic malignant syndrome in a hospital population. *Am J Psychiatry* 1991; **148**: 880–2

31 Kelkar VV, Jindal MN. Chlorpromazine-induced contracture of frog rectus abdominis muscle. *Pharmacology* 1974; **12**: 32–8

32 Krivosic-Horber R, Adnet P, Guevart E, Theunynck D, Lestavel P. Neuroleptic malignant syndrome and malignant hyperthermia. *Br J Anaesth* 1987; **59**: 1554–6

33 Lazarus A. Differentiating neuroleptic-related heatstroke from neuroleptic malignant syndrome. *Psychosomatics* 1989; **30**: 454–6

34 Levenson JL. Neuroleptic malignant syndrome. *Am J Psychiatr* 1985; **142**: 1137–45

35 Levinson DF, Simpson GM. The treatment and management of neuroleptic malignant syndrome. *Prog Neuropsychopharmacol Biol Psychiatr* 1992; **16**. 425–43

36 McCarron MM, Boettger ML, Peck JI. A case of neuroleptic malignant syndrome successfully treated with amantadine. *J Clin Psychiatr* 1982; **43**: 381–2

37 McCarthy A. Fatal recurrence of neuroleptic malignant syndrome. *Br J Psychiatr* 1988; **152**: 558–9

38 Miyatake R, Iwahashi K, Matsushita M, Nakamura K, Suwaki H No association between the neuroleptic malignant syndrome and mutations in the RYR1 gene associated with malignant hyperthermia. *J Neurol Sci* 1996, **143**: 161–5

39 Pope AG, Keck PE, McElroy SL. Frequency and presentation of neuroleptic malignant syndrome in a large psychiatric hospital. *Am J Psychiatr* 1986; **143**: 1227–33

40 Reyford HG, Cordonner C, Adnet PJ, Krivosic-Horber RM, Bonte CA. The in vitro exposure of muscle strips from patients with neuroleptic malignant syndrome cannot be correlated with the clinical features. *J Neurol Sci* 1990; **98** (Suppl 6.6): 527

41 Rosenberg MR, Green M. Neuroleptic malignant syndrome. review of response to therapy. *Arch Int Med* 1989; **149**: 1927–31

42 Sachdev P, Mason C, Hadzi-Pavlovic D Case–control study of neuroleptic malignant syndrome. *Am J Psychiatr* 1997; **154**: 1156–8

43 Shalev A, Munitz H. The neuroleptic malignant syndrome agent and host interaction. *Acta Psychiatr Scand* 1986; **73**· 337–47

44 Shalev A, Hermesh H, Munitz H. Mortality from neuroleptic malignant syndrome. *J Clin Psychiatr* 1989; **50**. 18–25

45 Takagi A Chlorpromazine and skeletal muscle: a study of skinned single fibers of the guinea pig *Exp Neurol* 1981; **734** 477–86

46 Tanii H, Taniguchi N, Niigawa H *et al.* Development of an animal model for neuroleptic malignant syndrome: heat-exposed rabbits with haloperidol and atropine administration exhibit increased muscle activity, hyperthermia and high serum creatine phosphokinase level. *Brain Res* 1996; **743**: 263–70

47 The European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia susceptibility. *Br J Anaesth* 1984; **56**: 1267–9

48 Thomas P, Maron M, Rascle C *et al.* Carbamazepine in the treatment of neuroleptic malignant syndrome. *Biol Psychiatr* 1998, **43**: 303–5

49 Tollefson G. A case of neuroleptic malignant syndrome. in vitro muscle comparison with malignant hyperthermia. *J Clin Psychopharmacol* 1982; **2**. 266–70

50 Toru M, Matsuda O, Makaguchi K. Neuroleptic malignant syndrome-like state following a withdrawal of antiparkinsonian drug. *J Nervous Mental Dis* 1981; **169**: 324–7

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Metabolic consequences of drug misuse

J. A. Henry

Academic Department of Accident and Emergency Medicine, Imperial College School of Medicine, St Mary's Hospital, London W2 1NY, UK

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Metabolic consequences of drug misuse are uncommon, but are increasing as illicit drug use becomes more widespread. Although the range of medical problems produced is very wide, metabolic problems most commonly occur with heroin, cocaine and the ecstasy group of drugs, which are therefore the main theme of this review.

Diamorphine (heroin)

Apart from cannabis, diamorphine is the most widely used illicit substance in Britain. Its respiratory depressant effects are well known, and the slowing of respiration caused by the drug can lead to an acute respiratory acidosis. Following an overdose, the patient may be cyanosed, comatose, miotic and bradycardic. Respiratory support may be needed urgently; reversal with naloxone is usually effective. The risk–benefit balance lies strongly in favour of naloxone administration, which has a diagnostic role as well as a useful therapeutic effect. There is a risk of precipitating agitation as a result of opioid withdrawal in an opioid-dependent individual, but this should not prevent its urgent administration. Adverse effects of naloxone are unusual. One publication has reviewed 453 cases in which naloxone was administered to heroin-dependent patients, and found a low incidence of complications (1.3%). These included immediate violence, pulmonary oedema, convulsions and asystole.[32] Anaphylactoid reactions can occur with some opioids, particularly codeine, and anaphylaxis may also occur as a result of contaminants in illicit heroin. One report has suggested that many heroin fatalities are caused by an anaphylactoid reaction, so that a significant number of deaths in heroin users may result from this cause.[12] One of the most serious consequences of non-fatal heroin overdose is the development of rhabdomyolysis, which may lead to renal failure. Alcohol, as well as being perhaps the most important precipitant of non-traumatic rhabdomyolysis, is also a cofactor in many cases of heroin-induced rhabdomyolysis.[8 14]

Other opioids, such as codeine and methadone, are implicated less commonly.[18 35] In general, rhabdomyolysis is a result of the heavy sedation produced as the patient lies comatose and motionless for a number of hours after an overdose of diamorphine. In most cases, lack of muscle tone and immobility appear to be sufficient to lead to rhabdomyolysis as a result of direct compression of skeletal muscle tissue. This mechanism is aggravated by hypoxaemia, acidosis, hypovolaemia and hypothermia, which often coexist in the deeply unconscious patient. However, it is also possible that a direct toxic effect is responsible, as rhabdomyolysis associated with heroin abuse has been linked to myocardial cell damage.[41] Cardiac damage and non-Q-wave myocardial infarction may also be caused by myocardial hypoperfusion.[29]

Rhabdomyolysis has also been reported in patients who have not experienced periods of unconsciousness.[14] In some cases, the damage may be severe enough to lead to renal failure requiring haemodialysis. Rarely, heroin-induced rhabdomyolysis can be complicated by other consequences of coma and pressure, leading to prolonged and incomplete recovery, as case reports have shown: myelitis, neuropathies and compartment syndromes can complicate the picture.[7 26] Compartment syndromes are not uncommon. Intracompartmental pressures should be measured when necessary, and fasciotomy may need to be performed.[24]

Once suspected, the diagnosis of heroin-induced rhabdomyolysis is usually straightforward. Occasionally there may be no symptoms in the conscious patient and, in a significant number of cases, there are no signs over the muscles indicating that damage has occurred.[14] Ultrasound may be helpful in confirming the diagnosis and location of the lesion by revealing hyperechoic areas within the muscles.[43] More commonly, muscle swelling and tenderness occur. If there is any significant degree of rhabdomyolysis, plasma aspartate transferase, alanine transferase, creatine kinase and lactate dehydrogenase concentrations increase markedly. The most serious biochemical complications are hyperkalaemia and hypocalcaemia.[45] Even at an early stage, large amounts of haem and myoglobin may be found in urine. Increasing plasma urea and creatinine concentrations indicate the onset of renal failure. Management consists of fluid replacement and early estab-

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lishment of adequate urine flow. Hyperkalaemia needs to be managed attentively, but excessive amounts of calcium should not be given during the hypocalcaemic phase in order to prevent later exacerbation of hypercalcaemia. If acute renal failure occurs, it should be managed conventionally.

Opioid withdrawal syndrome

After a few weeks of regular use, sudden withdrawal of diamorphine produces an influenza-like syndrome which begins 8–24 h after the last dose, reaches a peak by 36–72 h and resolves within 7–10 days. Symptoms include hypersecretion, sleeplessness, muscle aches, tremor, anxiety, nausea, vomiting, diarrhoea and abdominal cramps. Apart from reintroduction of an opioid, these symptoms respond to administration of drugs such as clonidine or lofexidine. However, in acute medical situations there may be a variety of reasons why an opioid drug should not be reintroduced. It is important for medical staff to be aware that opioid withdrawal can also be dealt with symptomatically, by administration of drugs such as diazepam or thioridazine for anxiety and agitation, beta blockade for tachycardia and hypertension, and loperamide for diarrhoea.

Heroin leucoencephalopathy

While most of the complications of heroin use tend to result from direct toxicity following intravenous use, a rare but dramatic complication occurs only after inhalation of heroin vapour ('chasing the dragon'): heroin is placed on aluminium foil, which is heated from beneath, and the resulting vapour is inhaled through a tube. A series of 47 patients was reported from the Netherlands in 1982,[49] 11 of whom died. Epidemiological studies showed that all had been using heroin in this way. All developed a severe illness, usually some days or even longer after the last heroin consumption, characterized by a cerebellar syndrome. Many had rigidity and hyperthermia. The pathological diagnosis was spongiform demyelination; the only other consistent abnormality was brown pigmentation of the alveolar macrophages in the lungs, probably related to the inhalation of hot vaporized heroin. A contaminant or pyrolysis product was suspected, but none was identified; several neurotoxic agents known to cause similar leucoencephalopathies were ruled out.

MDMA (ecstasy)

During the 1970s and early 1980s, 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) became increasingly popular as a 'recreational' drug in the USA. In at least one university, as many as 30–40% of students had tried it.[33] However, several MDMA-associated deaths were reported, mainly from cardiac arrhythmias,[10 44] though hyperthermia was also reported.[3] During the mid-1980s, MDMA use spread to Britain and, from there, to the rest of Europe, and also to Australia, being promoted mainly through clubs. In the UK, a remarkable development occurred. Ecstasy was introduced to the dance scene, and its use rapidly became epidemic. The main reason for this seems to lie in the pharmacological profile of the drug.[36] It is related to mescaline and lysergic acid diethylamide (LSD), which are hallucinogenic, but it does not produce the perceptual distortions associated with other hallucinogenic drugs. At the same time, the amphetamine-like effects of ecstasy provide an increase in physical and mental energy and minimize any feelings of tiredness, thus enabling the user to continue dancing for longer than may be safe for body systems.

Table 1 Reasons for hyperthermic collapse after MDMA ingestion

Prolonged exertion with minimal fluid replacement	Drug effects
Warm environment	Crowded clubs
Mood-enhancing effects of MDMA	Feeling of empathy, facilitates dancing
Amphetamine-like effects of MDMA	Euphoria, alertness; energy from sympathetic stimulation, disregard for body signals (thirst, tiredness, exhaustion)
Serotonergic effect of MDMA	Increased muscle tone leads to heat production

Two case reports of fatal hyperthermia following MDMA ingestion appeared in the British literature[5 6] and, in 1992, a series of seven fatal cases was reported.[16] A subsequent collation of literature reports[31] drew attention to the importance of a high body temperature as a predictor of a fatal outcome. The mean recorded temperature in fatalities was 41.6°C, compared with 40.5°C in the hyperthermic survivors. It seems apparent that cases of severe hyperthermia and deaths from heat stroke were mainly the result of prolonged dancing without rest and without taking enough liquid to enable normal temperature control by sweating[15] (Table 1). Collapse occurred, sometimes with convulsions. When examined in hospital, these patients tended to have a very high heart rate and a low arterial pressure, and had body temperatures as high as 43°C. Deaths have resulted, usually because the body cannot sustain the massive stress of high body temperature. As well as its amphetamine-like properties, the role of the serotonergic effect of the drug may be important in some cases, and may explain some fatalities where physical exercise was only minimal.

Convulsions, cardiovascular collapse, disseminated intravascular coagulation, rhabdomyolysis and acute renal failure are all complications of the gross thermal stress (see Table 2). Once disseminated intravascular coagulation has become established, management is difficult. This complication is the commonest reason for death in the hyperthermic patient who has taken MDMA. It is possible that an effect of MDMA on platelet function may also be responsible.

Table 2 Seven fatal cases of MDMA toxicity reported in 1992; DIC=disseminated intravascular coagulation

Case	Age and gender	Circumstances and amount	Clinical course	Outcome
1	18 M	Three tablets taken at club	Collapse, hyperthermia (41.8°C), tachycardia, hypotension, asystole	Died 2.5 h after admission
2	17 M	Two tablets taken at party	Coma, convulsions, hyperthermia (41°C) tachycardia, hypotension, DIC	Died 14 h after ingestion (11 h after admission)
3	18 M	Five tablets taken at party	Collapse, hyperthermia (42.1°C), gastrointestinal haemorrhage	Died 36 h after admission
4	16 F	One tablet taken at club	Hallucinating, hyperthermia (40°C), tachycardia, hypotension, metabolic acidosis, DIC	Died 36 h after admission
5	21 F	Two tablets taken at party	Convulsions, hyperthermia (41°C), tachycardia, hypertension, DIC	Liver transplant after 4 days, death from graft rejection after 18 days
6	20 M	Found collapsed in street after party; haemophiliac	Convulsions, hyperthermia (40°C), tachycardia, hypertension, DIC, rhabdomyolysis, acute renal failure	Died 60 h after admission
7	18 M	Took three tablets at pop concert	Convulsions, hyperthermia (43°C), tachycardia, hypotension, rhabdomyolysis, acute renal failure	Died 6.5 h after admission

Management of the hyperthermic patient

The main objectives are to facilitate thermoregulation and to prevent the development of disseminated intravascular coagulation. Full supportive care should be provided. An anticonvulsant, such as intravenous diazepam, may be needed if the patient is having convulsions. The most urgent priority is to restore intravascular volume, since extracellular fluid volume tends to be grossly depleted by prolonged sweating. A rapid 1 litre intravenous fluid challenge should reduce the pulse rate and increase arterial pressure. If the patient has a temperature of ≥40°C, or is not sweating, and has established heat stroke, the use of dantrolene may be indicated.[16] Management of the other acute complications follows standard medical practice.

Hepatic damage

In 1992, seven cases of hepatic damage associated with MDMA use were reported.[16] Several isolated cases have also been reported, including two cases of acute hepatitis[9 11] and one of accelerated hepatic fibrosis.[23] A series of 12 cases of hepatic damage has been reported from the Institute of Liver Studies at King's College Hospital,[13] where it was suggested that the incidence of ecstasy-induced hepatitis is increasing. A spectrum of severity seems to exist, with histological changes varying from a mild to moderate lobular hepatitis to features of massive hepatic parenchymal collapse with areas of nodular regeneration. An immunological mechanism appears to be the most likely cause of the sporadic cases of hepatitis which have occurred in ecstasy users. It is possible that, with the current degree of ecstasy use leading to repeated re-exposure, the incidence of cases of liver damage may increase with time.

Hyponatraemia

Once it became apparent that hyperthermia was a danger for ecstasy users, fluid replacement was advised. Some early harm-limitation messages indicated that ecstasy users should drink large amounts of fluids (but without specifying that the fluids were to replace fluid losses caused by prolonged exertion). Some people have become acutely ill and a small number have died from acute water intoxication. The causation can be largely explained by the popular misconception that water drinking is good for those taking ecstasy, together with the pharmacological properties of the drug.

Hyponatraemia is an uncommon complication of MDMA ingestion. Only a few cases have been reported.[19 22 27 28] The death of Leah Betts achieved wide publicity in the popular press, and it became clear that fatal water intoxication can be precipitated by excessive water drinking in ecstasy users. Fifteen cases were identified between August 1994 and December 1995 by the National Poisons Information Service (London), with serum Na^+ concentrations of <130 mmol litre^{-1}. The clinical pattern was remarkably uniform, with initial vomiting and disturbed behaviour, followed by drowsiness and agitation and, in seven cases, epileptiform convulsions. Drowsiness, a mute state and disorientation were observed for up to 3 days (Hartung TK, Schofield E, Short AI, Parr MJA, Henry JA, unpublished).

The neurological dysfunction is caused by haemodilution, with a rapid decrease in serum Na^+ concentration, leading to intracellular movement of water and, subsequently, to cerebral oedema. The patients developed severe illness within 12 h of ingesting ecstasy, suggesting that there is an acute drop in serum Na^+ concentration secondary to unrestricted fluid ingestion. The hyponatraemia appears to involve inappropriate secretion of antidiuretic hormone. One case of MDMA-induced hyponatraemia has been documented in which antidiuretic hormone concentrations were measured, and it was confirmed that concentrations of antidiuretic hormone were in fact inappropriately increased, the plasma arginine vasopressin concentration being 4.5 pmol litre^{-1}.[19] It has been shown more recently that secretion of antidiuretic hormone is markedly increased following administration of 40 mg MDMA in healthy volunteers.[15] It thus appears that this phenomenon is not an idiosyncratic effect of the drug, but is a predictable pharmacological effect. Thus, anyone taking MDMA who drinks large amounts of water without exercising and sweating is risking hyponatraemia with its attendant complications. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a well recognized phenomenon which may occur postoperatively[2] or after the administration of psychoactive drugs.[42] However, in most drug- or illness-induced cases, it arises gradually as a result of normal intake of fluid with restriction of output by antidiuretic hormone, whereas in ecstasy-associated cases, there has been an excessive intake of fluid within a short space of time. This results in an acute onset of symptoms, and it can occur with Na^+ concentrations which might not otherwise appear to be dangerously low. Most patients seem to make a steady recovery without neurological sequelae once they reach medical care. Fluid restriction is usually sufficient and any administration of fluids should be avoided if there is any suspicion of hyponatraemia, but the use of intravenous mannitol, loop diuretics or hypertonic saline may be considered.

Cocaine

Although historically well known as a topical anaesthetic for intranasal surgery, cocaine is now widely abused for its euphoriant effects. However, users pay the penalty of the challenge presented to body systems, and may suffer from headaches, sexual dysfunction, chronic cough (related to crack cocaine smoking), convulsions and cerebrovascular accidents. Cardiovascular complications include chest pain (the commonest mode of hospital presentation), cardiac arrhythmias, myocardial infarction (caused by the immediate effects on blood vessels and platelets as well as the result of accelerated atheroma),[20] myocarditis, dissecting aneurysm and sudden death. Prolonged recreational use may also lead to paranoia and violent, antisocial behaviour, including homicide and suicide Because of its powerful vasoconstrictor effect, snorting cocaine hydrochloride causes damage to nasal membranes and the nasal septal cartilage. Crack cocaine causes thermal damage to the airways, over and above its systemic effects.

In most cases, the effects of cocaine are relatively short-lived because its elimination half-life is 30–60 min, and the patient is usually asymptomatic within 2 h. However, heavy cocaine use may be associated with more prolonged symptoms and may lead to rhabdomyolysis or hyperthermia. Its unwanted metabolic effects derive from central nervous system stimulation resulting from blockade of dopamine re-uptake, so that the patient may be agitated, violent, hallucinating or convulsing. The exertion involved can generate heat, leading to hyperthermia and contributing to rhabdomyolysis. In addition, blockade of norepinephrine re-uptake leads to marked sympathomimetic effects as a result of alpha-1 and beta-1 stimulation. These include tachycardia and hypertension, but may also be responsible for the development of hyperthermia and rhabdomyolysis. The mode of use may be relevant: intravenous use is a risk factor for complications, as is the use of free base 'crack' cocaine, which is smoked and rapidly enters the circulation through the pulmonary vasculature. Crack cocaine may also be swallowed, with serious consequences.[30]

Seizures, hyperactivity, hypokalaemia, severe muscle contraction and hyperthermia may be important causes of rhabdomyolysis in cocaine intoxication. These may interact with ischaemia secondary to hypotension or vasoconstriction. The incidence of cocaine-associated rhabdomyolysis has not yet been defined, but there have been numerous case reports, and more cases are being seen with growing use of the drug.[47] One study found that 24% of patients attending an emergency department with cocaine toxicity had evidence of rhabdomyolysis, but most had no associated symptoms. A survey in Miami of 39 patients presenting with rhabdomyolysis after cocaine use, found a mean creatine kinase concentration of 12 187 u litre^{-1}. Thirteen had renal failure, seven of whom developed disseminated intravascular coagulation; six patients died.[38] The development of renal failure is not uncommon as a consequence of cocaine-induced rhabdomyolysis.[34] In occasional cases, renal failure may occur in the absence of rhabdomyolysis. Cocaine may also hasten progression to uraemia in patients with underlying renal insufficiency.

The amount of cocaine used does not predict the likelihood of a fatal outcome. Fatal blood concentrations in cocaine users who die from other causes, such as road traffic accidents, are similar to those who have died of cocaine toxicity.[21] Another factor whose relevance is not widely appreciated is the formation of cocaethylene, an ethyl homologue of cocaine which is formed in the liver

Table 3 Features of excited delirium

Phase	Clinical	Behavioural
1. Hyperthermia	Increased body temperature, profuse sweating	Attempts to cool body, removes clothes, goes into the open
2. Delirium	Paranoid behaviour, dilated pupils	Shouting, thrashing, violence, unexpected strength
3. Respiratory arrest	Collapse, cessation of breathing	Loss of strength
4 Death	Cardiorespiratory arrest	

only in the presence of ethanol. Cocaethylene has pharmacodynamically similar properties to cocaine; although it is metabolized along the same pathways as cocaine, its plasma elimination half-life is three to five times that of cocaine, so that the potential for accumulation to toxic levels is greater. This is probably why the risk of immediate death is 18- to 25-fold greater for ingestion of alcohol during use of cocaine than for use of cocaine alone.[1 4] Many binge users of cocaine drink relatively heavily during sessions because they are aware that this interaction prolongs the effects of cocaine use. Another factor which may influence the severity of symptoms in patients presenting with cocaine toxicity is the concentration of plasma cholinesterase (pseudocholinesterase). This enzyme is responsible for the detoxification of cocaine in the body, and it has been shown that patients with life-threatening cocaine toxicity had lower plasma cholinesterase activity than those who had non-life-threatening toxicity.[17] The low cholinesterase concentrations may be related to poorer nutritional status of regular cocaine users.

Early intervention with high-dose diazepam is probably the most effective first-line measure to prevent the progression of symptoms and ultimately to prevent rhabdomyolysis. Haloperidol or droperidol are not indicated as first-line drugs as they may increase the risk of seizures. Nitrates are appropriate for hypertension and, although beta-blockers may carry the risk of inducing alpha-adrenergic vasoconstriction, a short-acting beta-antagonist such as esmolol can be used. However, by the time the patient has presented, rhabdomyolysis may be established and conventional treatments will then be required to prevent the development of renal impairment or to manage established renal failure. Hyperpyrexia may be severe and the immediate management should include high-dose diazepam, urgent restoration of fluid balance and the administration of dantrolene.

Cocaine excited delirium

Apart from the effects of cocaine described above, an important but unusual complication of cocaine use, termed agitated delirium or excited delirium, began to be apparent during the epidemic of cocaine use in the USA in the 1980s.[48] It may well be an extreme form of cocaine toxicity.[40] Although it may rarely complicate mental or physical illnesses, it is most commonly associated with cocaine use. Emergency physicians, anaesthetists and intensive care staff should be aware of it, as cases are now occurring in Britain. It occurs in regular cocaine users who have used the drug within the last 24 h; there is no evidence that an overdose of cocaine has been taken and there is no readily apparent precipitating cause. Four elements occur in close succession: hyperthermia, agitated behaviour, collapse and death (Table 3). The number of self-limiting cases is unknown. The individual becomes aware of an increase in body temperature, sweats profusely and attempts to cool down by tearing off clothes and cooling himself with cold water. This stage merges into a phase of confusion and agitation. In many cases, the person wanders into the street shouting and behaving erratically. He may hide behind bushes or attack his image in mirrors or shop windows. After a period of time the individual becomes subdued and may die. Death frequently occurs after the police have been called and have been attempting to restrain the individual. When restraint is used, extreme strength is often apparent, and several people may be needed to maintain control. Body temperature, where it has been measured, is frequently >40°C, so hypermetabolism is clearly a feature of the illness.

A report from Florida has compared people who died from accidental cocaine overdose with those who had died from excited delirium. Compared with controls, those who died from excited delirium were more likely to be black, male and younger. They were less likely to have a low body mass index and more likely to have died in police custody, to have received medical treatment immediately before death, to have survived for a longer period. to have developed hyperthermia and to have died during the summer months.[39] Post-mortem blood concentrations of cocaine and its metabolites were similar to those in cocaine users who had died of other causes. The authors considered as a possible cause of excited delirium that chronic cocaine use disrupts dopaminergic function and that, when this is coupled with recent cocaine use, it may be sufficient to precipitate agitation, delirium, aberrant thermoregulation, rhabdomyolysis and sudden death. The most characteristic finding at post-mortem is that the dopamine receptor density in the striatum is not increased as it is in cocaine overdose.

There are currently no medical management guidelines for excited delirium. Physical restraint is clearly counterproductive, and may contribute to a fatal outcome in a hyperthermic, agitated patient, but is usually necessary in the interest of public safety. Once the patient reaches medical care, diazepam is the agent most likely to be of use, reducing neuronal excitability and acting as a pharmacological restraint. Urgent fluid replacement is probably of considerable importance, though there is, as yet, no evidence to support this.

Other drugs

Amphetamine sulphate has long been known as an occasional cause of hyperthermia and rhabdomyolysis. More recently, MDMA has overtaken it in Britain, mainly because of its association with dancing, but toxicity and deaths still occur. In the western USA, methamphetamine is commonly abused and abusers can present with agitation, violence, rhabdomyolysis and renal failure. Creatine kinase concentrations tended to be twice as high as with rhabdomyolysis from other causes.[37]

Phencyclidine is an important cause of rhabdomyolysis, but is very rarely used outside the USA. In one series of 1000 cases, 22 had rhabdomyolysis.[38] Cannabis is very widely used and has powerful pharmacological effects. However, metabolic complications are unusual. There is a single case report of hyperthermia following cannabis use, in which an individual developed hyperthermia after jogging.[46] Volatile substance abuse (solvent misuse) is a common means of intoxication in young people. Heavy exposure can lead to neuropathic damage, but chronic toluene exposure can also produce metabolic consequences. Toluene-induced renal tubular acidosis can cause hypokalaemia, increasing the risk of cardiac dysrhythmias and leading to hypokalaemic paralysis, rhabdomyolysis and renal calculi.[25]

Conclusion

Physicians, anaesthetists and intensive care staff need to be conversant with the clinical problems produced by illicit drugs. The metabolic problems are among the most taxing of these because they are usually associated with severe toxicity and because of the wide range of body systems involved. One of the key features of management is aggressive hydration for patients with hyperthermia and rhabdomyolysis.

References

1 Andrews PJ. Cocaethylene toxicity. *Addict Dis* 1997; **16**: 75–84

2 Arieff AI. Management of hyponatraemia. *Br Med J* 1993; **307**: 305–8

3 Brown C, Osterloh J. Multiple severe complications from recreational ingestion of MDMA ('ecstasy'). *JAMA* 1987; **258**: 780–1

4 Cami J, Farre M, Gonzalez ML, Segura J, de la Torre R. Cocaine metabolism in humans after use of alcohol. Clinical and research implications. *Recent Dev Alcohol* 1998; **14**: 437–55

5 Campkin NT, Davies UM. Another death from ecstasy. *J Roy Soc Med* 1992; **85**: 61

6 Chadwick IS, Curry PD, Linsley A, Freemont AJ, Doran B. Ecstasy, 3,4-methylenedioxymethamphetamine (MDMA), a fatality associated with coagulopathy and hyperthermia. *J Roy Soc Med* 1991; **84**: 371

7 Chan P, Lin TH, Luo JP, Deng JF Acute heroin intoxication with complications of acute pulmonary edema, acute renal failure, rhabdomyolysis and lumbosacral plexitis: a case report. *Chung Hua I Hsueh Tsa Chih (Taipei)* 1995, **55**: 397–400

8 Deighan CJ, Wong KM, McLaughlin KJ, Harden P. Rhabdomyolysis and acute renal failure resulting from alcohol and drug abuse. *Q J Med* 2000; **93**: 29–33

9 Deltenre P, Henrion J, Jacques JM, Schapira M, Ghilain JM, Maisin JM. Toxic hepatitis due to ecstasy administration. report of a possible case and literature review *Acta Gastroenterol Belg* 1994; **57**: 341–5

10 Dowling GP, McDonough ET, Bost RO 'Eve' and 'ecstasy'. A report on five deaths associated with the use of MDEA and MDMA *JAMA* 1987; **257**: 1615–17

11 Dykhuizen RS, Brunt PW, Atkinson P, Simpson JG, Smith CC. Ecstasy induced hepatitis mimicking viral hepatitis. *Gut* 1995, **36**: 939–415

12 Edston E, van Hage-Hamsten M. Anaphylactoid shock—a common cause of death in heroin addicts? *Allergy* 1997, **52**: 950–4

13 Ellis AJ, Wendon JA, Portmann B, Williams R. Acute liver damage and ecstasy ingestion. *Gut* 1996; **38**: 454–8

14 Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. *Medicine* 1982; **61**: 141–52

15 Henry JA, Fallon JK, Kiernan AT, Hutt AJ, Cowan DA, Forsling M. Low-dose MDMA ('ecstacy') induces vassopressin secretion *Lancet* 1998; **351**: 1784

16 Henry JA, Jeffreys KJ and Dawling S Toxicity and deaths from 3,4-methylenedioxymethamphetamine ('ecstasy'). *Lancet* 1992; **340**: 384–7

17 Hoffman RS, Henry GC, Howland MA, Weisman RS, Weil L, Goldfrank LR. Association between life-threatening cocaine toxicity and plasma cholinesterase activity. *Ann Emerg Med* 1992; **21**: 247–53

18 Hojs R, Sinkovic A. Rhabdomyolysis and acute renal failure following methadone abuse. *Nephron* 1992; **62**: 362

19 Holden R, Jackson MA Near-fatal hyponatraemic coma due to vasopressin over-secretion after 'ecstasy' (3,4-MDMA). *Lancet* 1996; **347**: 1052

20 Judd E, Hollander MD. Cocaine-associated myocardial infarction. *J Roy Soc Med* 1996: **89**: 443–7

21 Karch SB, Stephens B, Ho CH, Relating cocaine blood concentrations to toxicity—an autopsy study of 99 cases *J Forensic Sci* 1998; **43**: 41–5

22 Kessel B. Hyponatraemia after ingestion of 'ecstasy'. *BMJ* 1994; **308**: 414

23 Khakoo SI, Coles CJ, Armstrong JS, Barry RE Hepatotoxicity and accelerated fibrosis following 3,4-methylenedioxymethamphetamine ('Ecstasy') usage. *J Clin Gastroenterol* 1995, **20**: 244–7

24 Klockgether T, Weller M, Haarmeier T, Kaskas B, Maier G, Dichgans J. Gluteal compartment syndrome due to rhabdomyolysis after heroin abuse *Neurology* 1997; **48**: 275–6

25 Kumar R, West DM, Jingree M, Laurence AS Case report Unusual consequences of heroin overdose: rhabdomyolysis, acute renal failure, paraplegia and hypercalcaemia. *Br J Anaesth* 1999; **83**: 496–8

26 Kroeger RM, Moore RJ, Lehman TH, Giesy JD, Skeeters CE. Recurrent urinary calculi associated with toluene sniffing. *J Urol* 1980; **123**: 89–91

27 Matthai SM, Davidson DC, Sills JA, Alexadrou D. Cerebral oedema after ingestion of MDMA ('ecstasy') and unrestricted intake of water. *BMJ* 1996; **312**: 1359

28 Maxwell DL, Polkey MI, Henry JA. Hyponatraemia and catatonic stupor after taking 'ecstasy'. *BMJ* 1993, **307**: 1399

29 Melandri R, Re G, Lanzarini C, Rapezzi C, Leone O, Zele I, Rocchi GJ. Myocardial damage and rhabdomyolysis associated with prolonged hypoxic coma following opiate overdose. *Clin Toxicol* 1996; **34**: 199–203

30 Merigan KS, Park LJ, Leeper KV, Browning RG, Giometi R. Adrenergic crisis from crack cocaine ingestion: report of five cases. *J Emerg Med* 1994; **12**: 485–90

31 O'Connor B. Hazards associated with the recreational drug 'ecstasy' *Br J Hosp Med* 1994; **52**: 507–14

32 Osterwalder JJ. Naloxone. Intoxications with intravenous heroin and heroin mixtures—harmless or hazardous? A prospective clinical study. *Clin Toxicol* 1996; **34**: 409–16

33 Peroutka SJ. Incidence of recreational use of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) on an undergraduate campus. *N Engl J Med* 1987; **317**: 1542–3

34 Pogue VA, Nurse HM, Cocaine-associated acute myoglobinuric renal failure. *Am J Med* 1989; **86**: 183–6

35 Pokorny CS, Saunders JB. Codeine induced rhabdomyolysis. *Aust N Z J Med* 1994; **24**: 582

36 Randall T. Ecstasy-fueled 'rave' parties become dances of death for English youths. *JAMA* 1992; **268**: 1505–6

37 Richards JR, Johnson EB, Stark RW, Derlet RW. Methamphetamine abuse and rhabdomyolysis in the ED: a 5-year study. *Am J Emerg Med* 1999; **17**: 681–5

38 Roth D, Francisco J Alarcon FJ, Fernandez J *et al.* Acute rhabdomyolysis associated with cocaine intoxication. *N Engl J Med* 1988; **319**: 673–7

39 Ruttenber AJ, McAnnaly HB, Wetli CV. Cocaine-associated rhabdomyolysis and excited delerium: different stages of the same syndrome. *Am J Forensic Med Pathol* 1999; **20**: 120–7

40 Ruttenber AJ, Lawler-Heavner J, Yin M, Wetli CV, Hearn WL, Mash DC. Fatal excited delirium following cocaine use: epidemiologic findings provide new evidence for mechanisms of cocaine toxicity. *J Forensic Sci* 1997; **42**: 25–31

41 Schwartzfard L, Singh G, Marcus D. Heroin-associated rhabdomyolysis with cardiac involvement. *Arch Intern Med* 1977; **137**: 1255

42 Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; **12**: 209–25

43 Steeds RP, Alexander PJ, Muthusamy R, Bradley M. Sonography in the diagnosis of rhabdomyolysis. *J Clin Ultrasound* 1999; **27**: 531–3

44 Suarez RV, Reimersma R. 'Ecstasy' and sudden cardiac death. *Am J Forensic Med Pathol* 1988; **9**: 339–41

45 Veenstra J, Smit WM, Krediet RT, Arisz L. Relationship between elevated creatine phosphokinase and the clinical spectrum of rhabdomyolysis. *Nephrol Dial Transplant* 1994; **9**: 637–41

46 Walter FG, Bey TA, Ruschke DS, Benowitz NL. Marijuana and hyperthermia. *Clin Toxicol* 1996; **34**: 217–21

47 Welch RD, Todd K, Drause GS. Incidence of cocaine associated rhabdomyolysis. *Ann Emerg Med* 1984; **13**: 1145–7

48 Wetli CV, Fishbain DA Cocaine-induced psychosis and sudden death in recreational cocaine users. *J Forensic Sci* 1985; **30**: 873–80

49 Wolters EC, van Wijngaarden GK, Stam FC *et al.* Leucoencephalopathy after inhaling 'heroin' pyrolysate. *Lancet* 1982; **ii**: 233–7

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Porphyrias

M. F. M. James* and R. J. Hift

Departments of Anaesthesia and Medicine, University of Cape Town and Groote Schuur Hospital, South Africa

**Corresponding author: Department of Anaesthesia, University of Cape Town Medical School, Anzio Road, Observatory 7925, Cape, South Africa*

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The porphyrins play a critical role in biology, being involved in a wide range of reactions related to oxygen utilization, transport, storage or formation. The synthetic pathway involved in the production of the porphyrins is complex and is governed by a sequence of enzymes. A defect in any of these enzymes results in accumulation of the preceding intermediaries and produces one form or another of the diseases known as the porphyrias. This review briefly outlines porphyrin synthesis, the diseases that arise from errors in porphyrin metabolism and the anaesthetic implications of these disorders.

Porphyrin metabolism

The porphyrins are cyclic structures formed by the linkage of four pyrrole rings through methene (–CH=) bridges. The porphyrin ring can, via the nitrogen atom of the pyrrole subunits, form complexes with many metals, giving metalloporphyrins. These compounds are widely distributed throughout the plant and animal kingdoms where they are essential for photosynthesis, oxygen transport, electron transport, the reduction of molecular oxygen and various hydroxylation reactions. Of the metalloporphyrins, the most biologically important are those containing iron (to form haem) and magnesium (to form chlorophyll). The porphyrins are highly coloured and exhibit red fluorescence in ultraviolet light. The porphyrin precursors, the porphyrinogens, which are linked by methyl (CH_2) bridges (Fig. 1), are colourless. When exposed to light and oxygen, they spontaneously convert to porphyrins.

In human physiology, haem is the most important of the porphyrins. In its biologically active form, haem is bound to various proteins to form haemoproteins, which include haemoglobin, myoglobin and all of the cytochromes (including the P_{450} series) together with numerous other compounds involved in oxidation and hydroxylation reactions.

The biosynthesis of haem commences with formation of δ-aminolaevulinic acid (ALA) by the condensation and subsequent decarboxylation of two freely available molecules—succinyl co-enzyme A (succinyl CoA) and the amino acid glycine—in a step catalysed by the enzyme ALA synthetase. This process occurs in the mitochondria (where succinyl CoA is produced in the citric acid cycle); ALA synthetase appears to be the most important rate-limiting enzyme in porphyrin biosynthesis. The next step in porphyrin biosynthesis occurs outside the mitochondria where two molecules of ALA condense under the influence of the enzyme ALA dehydratase to form the monopyrrole subunit of the porphyrin ring, porphobilinogen (PBG) The enzyme PBG deaminase catalyses the condensation of four molecules of PBG to form hydroxymethylbilane, which is then converted into the first of the porphyrinogens, uroporphyrinogen, under the influence of uroporphyrinogen cosynthetase. The stepwise decarboxylation and conversion of uroporphyrinogen acetate groups to methyl substituents results in the formation of coproporphyrinogen which then re-enters the mitochondria where oxidation and chelation with ferrous iron result in the production of haem. These steps together with the relevant enzymes are illustrated in Fig. 2. The porphyrin biosynthetic pathway operates very efficiently and <2% of the porphyrin precursors are produced in excess of that required for haem synthesis. Consequently, the finding of increased concentrations of porphyrin intermediates in urine or stool indicates an abnormality of production, with a partial block somewhere in the enzymatic chain.

Control of haem biosynthesis

The control of the production of haem is effected primarily through ALA synthetase. This enzyme has a low endogenous activity and also has a very short half-life, making it ideally suited to a regulatory role. The formation of ALA

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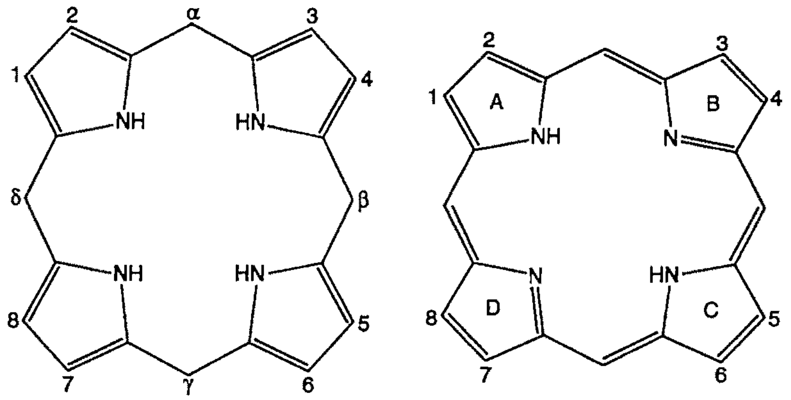

Fig 1 The structures of the porphyrinogens (left) and porphyrins (right) Substituents are numbered according to the conventional Fisher system. In the porphyrinogen ring, the positions designated by Greek letters are occupied by methyl groups $(-CH_2)$, whereas in the porphyrin ring these positions are occupied by methene $(-CH=)$ groups. The colourless porphyrinogens undergo spontaneous conversion to purple-coloured porphyrins on exposure to light and air, hence the characteristic urine colour change, when urinary porphyrinogens are present, from normal to a 'port wine' appearance on standing.

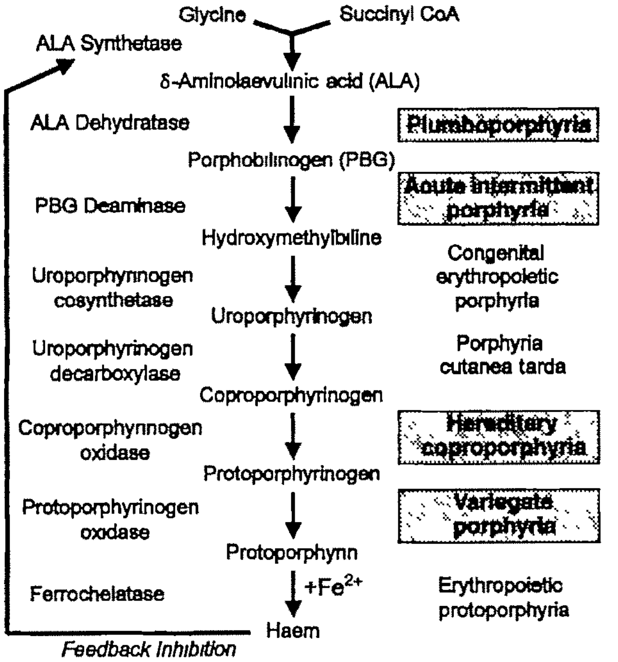

Fig 2 Metabolic pathways of haem synthesis. The enzymes involved at each step are listed on the left, and the type of porphyria associated with a deficiency of each enzyme is shown on the right The conditions highlighted in boxes are the acute porphyrias.

synthetase is controlled by the concentration of haem itself, which forms a negative feedback loop, thus ensuring that the level of haem production matches requirements closely. The concentration of haem required to suppress enzyme *production* is extremely low, of the order of 10^{-7} M, while that required to inhibit enzyme *activity* is of the order of 10^{-5} M. However, the concentration of haem generated within the mitochondrion is insufficient to inhibit the enzyme, so ALA synthetase control is thought to be exerted by a volatile 'free haem pool' within the cytosol.[38] It is also possible that some measure of control is exerted by the availability of glycine.

ALA synthetase is readily inducible and can respond rapidly to increased haem requirements such as those resulting from the administration of drugs which require cytochrome P_{450} for their metabolism. Thus the availability and activity of the enzyme depend on the intracellular level of haem, and the demand for haem by metabolic processes. This fact is of great relevance in the development of the porphyrias, in which an increase in haem requirements in the face of a partial block in the synthetic pathway results in the overproduction of ALA synthetase, and consequently of the pathway intermediates before the block. The enzyme PBG deaminase also seems to have a regulatory role that is of relevance in some porphyric conditions. Under normal circumstances, an increase in production of ALA results in an increase in activity of PBG deaminase, thus enabling the synthetic pathway to continue efficiently. However, in acute forms of the disease, there appears to be a concomitant failure of PBG deaminase to respond appropriately, with a resultant accumulation of the early components of the metabolic pathway. Recent work has shown that coproporphyrinogen and protoporphyrinogen, both of which are produced in excess in variegate porphyria, can also inhibit PBG deaminase.[34]

Classification of the porphyrias

The porphyrias can be classified by the main site of the defect (hepatic or erythropoietic), by the enzyme defect (Fig. 2) or by whether or not they cause acute symptoms (Table 1). The latter method of classification is particularly useful for anaesthetic practice as only the acute forms of the porphyrias are of major anaesthetic relevance, since these are the conditions that may result in life-threatening reactions to drugs. All the hepatic porphyrias except for porphyria cutanea tarda are acute porphyrias.

Table 1 Classification of the porphyrias

Type of porphyria	Examples
Acute	acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HC), plumboporphyria (PP)
Non-acute	porphyria cutanea tarda (PCT); erythropoietic porphyrias: congenital erythropoietic porphyria (CEP); erythropoietic protoporphyria (EPP)

The acute porphyrias

The acute porphyrias include acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP) and the very rare plumboporphyria (PP). With the exception of PP, which is recessive, these porphyrias are inherited as non-sex-linked, autosomal dominant conditions with variable expression. Like many inherited conditions, they have a patchy distribution. The overall frequency of AIP in Europe is estimated to be one per 20 000, with one per 10 000 in Northern Sweden and an even higher incidence in Lapland. VP is particularly common in the Afrikaner community in South Africa where the prevalence has been estimated at between one in 250 and one in 500,[12] but the disease is recognized worldwide and in Britain is thought to be about a third as prevalent as AIP.[17] The true incidence of these conditions is hard to estimate as many individuals remain asymptomatic throughout their lives; this is particularly true of HCP where more than half the affected individuals may be symptom-free.

The enzyme defects in porphyria are deficiencies rather than absolute deficits. In most patients with clinically expressed porphyria, the level of enzyme reduction is generally of the order of 50%,[26] suggesting that the defective allele produces essentially no enzyme activity. This may be why homozygotes are extremely rare, as complete failure to produce haem is probably incompatible with life. Increasingly, however, families are being identified in which mutations appear to encode proteins with some residual activity. Where such a family marries into another carrying a more typical mutation for the same defect, compound heterozygotes may result; such patients express low levels of enzyme and characteristically are phenotypically severely affected. Although there is no direct influence of gender on the pattern of inheritance, attacks occur more frequently in women and are most frequent in the third and fourth decades. Few cases have been reported before puberty, and attacks are rare after the menopause,[29] although presentation has occurred between the ages of 7 and 75 yr.[27] Acute attacks of porphyria are most commonly precipitated by events that decrease haem concentrations, thus increasing the activity of ALA synthetase and stimulating the production of porphyrinogens. Acute exacerbations may be precipitated by a number of factors, including physiological hormonal fluctuations (such as those occurring with menstruation), fasting, dehydration, stress and infection.[14] Though pregnancy was thought to represent a particular risk in the porphyric patient, with acute attacks reportedly occurring in a high proportion of pregnant patients (24–95%) with AIP,[29] more recent experience suggests that the rate in pregnancy is lower. Frequent spontaneous abortion (6–12%) and hypertension may, however, complicate pregnancy in the patient with AIP and there is an increased incidence of low-birthweight infants. Nevertheless, enzyme-inducing drugs are by far the most important trigger factors, particularly in relation to anaesthesia.

Acute attacks are characterized by severe abdominal pain, autonomic instability, electrolyte disturbances and neuropsychiatric manifestations; they may range from a mild disturbance to fulminating attacks with a fatal outcome.[17] Neuromuscular weakness, which may progress to quadriparesis and respiratory failure, is the most prominent and potentially lethal neurological manifestation, but sensory losses also occur. Central nervous system involvement with upper motor neuron lesions, cranial nerve palsies and involvement of the cerebellum and basal ganglia are less commonly seen. Permanent neurological lesions, especially parasympathetic dysfunction, can occur, particularly in AIP, although this is rarely seen unless the attacks have been multiple or of long duration. Though psychiatric disturbances were believed to occur in a high percentage of overt sufferers from the condition, the current belief is that these have been greatly exaggerated. Seizures may occur during an acute attack. Gastrointestinal symptoms are the most common and typically present with severe abdominal pain with vomiting and occasionally diarrhoea. Clinical examination of the abdomen is remarkably normal considering the severity of the symptoms,[15] since there is no peritonism. Abdominal pain is thought to relate directly to the autonomic neuropathy, though there may be a contribution from abnormal bowel function with alternating areas of spastic and relaxed bowel. Ganglionic blockade may, therefore, be helpful in this condition,[6] though it is seldom necessary, since the abdominal complaints commonly abate promptly with resolution of the attack. Dehydration and electrolyte abnormalities of Na^+, K^+ and Mg^{2+} may be severe and careful fluid and electrolyte management is essential. Cardiovascular instability—with tachycardia and arterial pressure changes of hypertension or, less commonly, hypotension—occurs, particularly in AIP, and permanent hypertension may result.

Between attacks, complete remission is the norm, and many subjects with the genetic defect remain asymptomatic. This is particularly important when planning a drug regimen in patients potentially at risk, as patients with so-called 'silent' (or latent) porphyria may have their first symptoms precipitated by injudicious administration of triggering agents. In all the acute porphyrias, acute attacks are characterized by markedly increased concentrations of ALA and PBG in the urine, though in PP the elevation is limited to ALA since the enzyme defect here lies before the step in which PBG is synthesized.

Drugs may trigger an acute attack of porphyria in many ways, most of which depend on an increased demand for haem production or a failure of haem inhibitory feedback as the final common pathway. Thus drugs may induce the transcription of ALA synthetase directly through mRNA or may interfere with the negative feedback control which haem exerts on ALA synthetase production. Drugs may interfere with the haem synthetic pathway, thus reducing the level of haem production, or they may increase the demand for haem by increasing utilization, for example through increased demand for oxidative processes mediated through the cytochromes. This multitude of potential pathways and the great variety of drug structures make it impossible to predict which agents are likely to be porphyrinogenic. The only properties of drugs which are clearly linked to porphyrinogenicity are lipid solubility[11] and membrane fluidization.[42] Some chemical groupings, such as the allyl groups which form the basis of the barbiturates, and certain steroid structures have also been incriminated in the induction of porphyria (steroids can enhance the induction of ALA synthetase). It is of interest that it is only the acute forms of the disease that are affected by enzyme induction, so this is the only form of the disease of pharmacogenetic importance. It is not clear why the manifestations of the non-acute forms of porphyria are not apparently affected by enzyme-inducing drugs. Even such potent inducers of ALA synthetase as the anticonvulsants do not exacerbate or precipitate porphyria cutanea tarda (PCT) or the erythropoietic porphyrias. The only apparent drug association with PCT is that of oestrogen-containing compounds. They may exacerbate the biochemical and skin manifestations of this condition, but acute attacks are never encountered in PCT. There are occasional reports of other agents being implicated in either the causation or exacerbation of the non-acute porphyrias, but Moore and colleagues concluded that the evidence for induction of these conditions by drugs other than oestrogens is weak.[38]. These conditions will, therefore, not be considered further. For more information about the non-acute porphyrias, see the review by Paslin.[45] Notably, there is no excess excretion of ALA or PBG in these conditions, whereas these changes are the hallmarks of the acute porphyrias.

The pathogenesis of the acute porphyrias is unclear, although there are several possibilities. The excessive production of ALA is common to all of the acute forms and in all but the very rare plumboporphyria there is a defect in PBG deaminase, either in terms of an absolute reduction of enzyme activity, or in terms of a failure to increase its level in response to increased demand. Thus it is possible that ALA or PBG, or both, may be directly neurotoxic, although the severity of the symptoms does not correlate well with the increase in either of these substances. Nevertheless, the accumulation of these two compounds appears likely to have some effect on symptomatology. An alternative, but not exclusive, hypothesis is that the failure of haem production results in an acute haem deficiency within the nerve cell, and that this is the chief cause of the neuronal lesions, although the toxicity of ALA and PBG may still be relevant.[38] It has also been suggested that haem deficiency results in a secondary reduction in the activity of haem-containing enzymes such as tryptophan oxygenase, with consequent disturbances in the production and metabolism of potential neurotransmitters such as serotonin.

Acute intermittent porphyria

The defective enzyme in this condition is porphobilinogen deaminase and the gene encoding this enzyme is located on chromosome 11. PBG deaminase deficiency can, in most cases, be detected in red cells between attacks. Of all the porphyrias, this one produces the most severe symptoms, and is the one in which an acute attack is most likely to be fatal. It has been reported that hypertension and impaired renal function are significantly more common in porphyric subjects than in their non-porphyric relatives, and that hypertensive complications and renal failure are the most frequent causes of death in patients with porphyria.[9]

Variegate porphyria

This condition is characterized by cutaneous photosensitivity in which bullous skin eruptions occur on exposure to sunlight as a result of the conversion of porphyrinogens to porphyrins. The characteristic skin lesion is one of excessive fragility, especially on sun-exposed surfaces such as the face and hands, where bullae and erosions with subsequent pigmented 'tissue paper' scarring are frequently seen. The name of this condition derives from the fact that patients may present with the skin manifestations associated with the non-acute porphyrias, or the disorders characteristic of AIP or combinations of both. The enzyme defect is at the level of protoporphyrinogen oxidase but there is also a reduced amount of PBG deaminase. The gene encoding this enzyme is on chromosome 1. The incidence of VP in South Africa is the highest in the world: in some areas it may be as high as one in 250 of the white population.[12] This has been shown to result from the introduction of a single point-mutation by a Dutch settler in 1688.[35]

Hereditary coproporphyria

This condition is far less common than VP and AIP. Acute attacks appear to be considerably less severe, and the prognosis better. The defective enzyme is coproporphyrino-

Table 2 Summary of major biochemical findings in the acute porphyrias Note that the findings described in the quiescent phase apply only to those with biochemically expressed disease, silent carriers will demonstrate no abnormality on urine and faecal testing, yet carry the gene and are at risk of an acute attack

Disorder	Phase	Urinary ALA and PBG	Urinary porphyrins	Faecal porphyrins
AIP	quiescent	increased	mild increase	normal
	acute	very high	very high	as above
HCP	quiescent	normal	coproporphyrin III often increased	increased coproporphyrin III
	acute	high	increased	as above
VP	quiescent	normal	normal	increased pentacarboxylic porphyrin III, coproporphyrin III and protoporphyrin IX
	acute	high	high	as above

gen oxidase, encoded by a gene on chromosome 9. As in VP, cutaneous photosensitivity is characteristic, though it tends to be less severe in the interval between acute attacks than it is in VP.

Plumboporphyria

This, the rarest of the acute porphyrias, results from a deficiency of ALA dehydratase, which is encoded by a gene on chromosome 9. It is associated with an excess of urinary ALA analogous to that found in lead poisoning (hence the name), although lead concentrations in the blood are normal. Unlike the other acute porphyrias, the mutation is recessive, and the disease presents early in life, with all clinically manifest cases being homozygotes.[19] No references to anaesthesia for patients with this condition have been published.

Implications for anaesthesia

It might be expected that the cytochrome-mediated metabolism and high lipid solubility of many anaesthetics would make many of them porphyrinogenic, and anaesthesia has certainly been implicated in the triggering of a number of severe porphyric reactions. Nevertheless, most porphyrics can be anaesthetized with relative safety provided that appropriate precautions are taken. The mainstay of safe anaesthetic management of the porphyric patient depends on the detection of susceptible individuals, and the identification of potentially porphyrinogenic agents. Neither of these is simple or readily achievable.

Identification of susceptible individuals

Laboratory identification of porphyric subjects is not easy, as many of them show only subtle or even no biochemical abnormalities during asymptomatic phases. The identification of potentially porphyric patients must, therefore, begin with knowledge of the local prevalence of the condition and then rely on the recognition of a suggestive personal or family history. Any suggestion of porphyria in the patient's history should be taken seriously and appropriate laboratory investigations undertaken. Where the urgency of the situation precludes full biochemical evaluation, the patient should be managed with an anaesthetic technique appropriate for a porphyric patient. The most appropriate test for the diagnosis of porphyria will vary according to the type of porphyria expected and the patient's circumstances. Thus, when the actual mutation is known in the family, DNA analysis is most appropriate. In the absence of this knowledge, determination of erythrocyte PBG activity is probably the most appropriate screening test for patients with suspected AIP, as detection of elevated ALA and PBG in urine is less sensitive. In the case of possible VP, HCP or a suspected acute attack, biochemical analysis of urine, stool and plasma porphyrin profiles is indicated. Direct enzyme activity estimates are problematic in these patients, because activity is expressed not in erythrocytes but only in nucleated cells such as fibroblasts or leukocytes, and then in such low amounts that standard assays are unreliable. The biochemical tests vary in their ability to identify porphyric patients depending on the type of the condition and whether or not the individual is in remission or suffering an attack; their interpretation is listed in Table 2. It must be remembered that prepubertal children who carry the gene will be asymptomatic, but are still at risk from an acute attack if improperly managed.[45]

Identification of drugs

The identification of drugs likely to be hazardous to the porphyric patient is also far from clear-cut. The labelling of drugs as safe or unsafe in porphyria is based on anecdotal experience of the use of the agents in porphyric patients and reports of the induction of acute attacks, or on measurements of porphyrins or their precursors in urine or faeces. Drugs may be tested for in cell culture models for their ability to induce ALA synthetase activity or for effects on porphyrin synthesis. Alternatively, their actions on the porphyrin synthetic pathway in animal models of porphyria can be investigated; in these models, porphyria is mimicked by administering known porphyrinogenic agents, such as the enzyme-blocking drug dicarbethoxy-dihydrocollidine (DDC). Both cell culture and animal models tend to overestimate the porphyrinogenicity of drugs. A summary of anaesthetic drugs for their perceived safety has been published previously.[22] However, as there are often conflicting reports of the safety of anaesthetic drugs in clinical

Table 3 Recommendations applied to drugs in the Porphyria Drug Safety Database

Category	Description
Use	The drug is likely to be safe and may be used freely.
Use with caution (UWC)	Though safety is not established beyond doubt, the evidence suggests that the drug is unlikely to prove unsafe in practice It may be used provided no safer alternative is available or suitable
Use with extreme caution only (UWECO)	There is evidence to suggest that the drug may yet prove unsafe in practice, or grounds to suspect this may be so, or too little evidence to suggest that it may be safe Such drugs should only be used if the expected benefits strongly outweigh the risks, and an adverse outcome must be anticipated
Avoid	There is evidence that such drugs have precipitated acute attacks in patients, or other grounds for believing that the risk of an acute attack is high
No data/avoid (ND/avoid)	There is too little evidence to draw a conclusion, and it is wisest to regard the drug as potentially hazardous and avoid its use.

practice, and since other factors such as infection or stress may precipitate a porphyric crisis coincidentally with the administration of anaesthesia, it is extremely difficult to assess the porphyrinogenic potential of anaesthetic agents with precision. Thus, any attempted classification of anaesthetic agents with regard to their porphyrinogenicity is far from ideal, and inevitably somewhat arbitrary.

In view of the difficulties clinicians experience in interpreting such terms as 'possibly safe' and 'probably unsafe' in drug lists, the Porphyria Drug Safety Database held at the University of Cape Town has been reviewed and modified to reflect the terms listed in Table 3, which give a clearer indication of the relative desirability of drugs. Those drugs most applicable to anaesthesia are listed in Table 4. The information presented in this table was obtained by examining data from the literature (itself based on clinical experience as well as animal and *in vitro* experiments), from personal experience and by the examination of drugs for structure, structural similarity and routes of metabolism. As such it represents both compromise and intuition unsubstantiated by hard data, and the recommendations cannot be guaranteed to prove valid under all circumstances. The list should serve as a guide only, and the authors cannot accept responsibility for errors or for any adverse experience. More information on specific agents may be obtained from the authors.

In general, drugs should be selected in the order Use, UWC, UWECO, ND/avoid and Avoid. Particular care must be taken when prescribing drugs for patients with AIP or clinically active forms of porphyria and when prescribing drugs in combination. Aggravation of porphyria is more likely under these circumstances.

Anaesthetic management

Any patient in whom porphyria is suspected requires a careful history, including a detailed family history, and thorough physical examination, including a careful neurological assessment, paying particular attention to the presence or absence of peripheral neuropathy and autonomic instability.[1] Note, however, that in the vast majority of patients, there will be no clinical evidence of the disease other than possible skin lesions (which are often subtle) in those with VP and, in the rare patient who has had previous acute attacks, some evidence of neuropathy.

If an acute crisis is suspected, particular attention must be paid to muscle strength and cranial nerve function, as symptoms related to these areas may predict impending respiratory failure or an increased risk of aspiration. Cardiovascular examination may reveal hypertension and tachycardia; these should be treated before anaesthesia. Respiratory muscle function may be compromised, and respiratory function tests may be indicated. In an acute crisis, postoperative ventilation may be required. During an acute exacerbation, the possibility of non-surgical abdominal pathology must always be suspected, with a high index of suspicion in a patient in whom the severity of symptoms is not matched by clinical findings. Preoperative preparation in a patient with an acute porphyric crisis must include the careful assessment of fluid balance and electrolyte status.

Premedication

Most (but not all) benzodiazepines commonly used for premedication are considered safe. The phenothiazines may have particular advantages. Good anxiolysis has been recommended as advantageous.[1] Where antacid administration is considered appropriate, sodium citrate may be given and ranitidine may be considered. Cimetidine has been recommended in the treatment of acute porphyric crises, since it may decrease haem consumption and inhibit ALA synthetase activity.[27] However, although it may be used safely as an H_2 receptor antagonist, it does not appear to be effective prophylactic therapy.[27] Preoperative starvation should be minimized; if a prolonged fast is unavoidable, a dextrose–saline infusion should be given during the preoperative period, since calorie restriction has been linked with the precipitation of acute attacks. In view of the frequency with which hyponatraemia is encountered in acute attacks, intravenous fluids containing dextrose alone should be avoided.

Regional anaesthesia

There is no absolute contraindication to the use of regional anaesthesia in the porphyric patient. However, careful examination and evaluation of the neurological status of the patient before the performance of a regional block is essential. Cardiovascular stability may be compromised by hypovolaemia and autonomic neuropathy.

Theoretically, lidocaine, which has been shown to be potentially porphyrinogenic in both of the commonly used animal models, should be considered unsafe. However, wide experience with the agent has not shown significant problems either when used as a local anaesthetic or when used intravenously for the control of arrhythmias, although experience with the latter usage is limited. On the basis that a worsening of the neuropathy might be ascribed to epidural anaesthesia, fear of litigation has been raised as an argument against the use of regional blockade.[26] However, as there is no evidence that any local anaesthetics have ever induced an acute attack or neurological pathology in porphyric subjects, there seems no good reason to avoid their use. This view is supported by a report of two instances of the use of regional anaesthesia in AIP during pregnancy in both of which bupivacaine (one epidural and one spinal administration) was used without complication.[32] The authors concluded that there was no evidence that general anaesthesia was safer for the pregnant porphyric patient than regional anaesthesia. In theory, procaine is the best agent to use, but in practice bupivacaine appears to be safe, and the intrathecal route, in which a minimum of agent is injected, seems ideal. The epidural use of procaine and fentanyl in a pregnant porphyric patient has been reported.[28] Böhrer and Schmidt[4] reported two cases managed with local anaesthesia and concluded that regional or local anaesthesia with bupivacaine, prilocaine, tetracaine or procaine may be the technique of choice for porphyric patients whenever the technique was applicable. However, problems with haemodynamic instability, mental confusion and associated neuropathy probably preclude the use of regional anaesthesia in the presence of an acute porphyric crisis,[1,27] although there are no studies specific to this issue.

General anaesthesia

The total dose of drug administered and the length of time for which the patient is exposed to the drug may influence the probability of triggering a porphyric crisis. The current availability of very short-acting anaesthetic agents almost certainly contributes to the increased safety of most modern anaesthetic techniques, although there are still some areas of controversy.

Induction. The barbiturates are the archetypal inducers of ALA synthetase, and all barbiturates, including thiopental, must be considered unsafe. Although there are numerous reports of the safe use of thiopental in porphyric patients in the quiescent phase,[53] seven out of 10 patients in acute porphyric crisis had their symptoms worsened following induction of anaesthesia with thiopental.[40] Thus, although thiopental will not always precipitate a crisis, all barbiturates must be considered contraindicated in porphyric patients. Etomidate is potentially porphyrinogenic in animal models[23] and at least one crisis has followed its use in human subjects, although its safe use has also been reported;[18] on balance, etomidate should probably be considered unsafe. Ketamine is probably safe; it has been used safely in quiescent AIP;[2,47,52] its safe use during a crisis in HCP has been reported,[7] and most animal and cell culture models suggest that it is non-inducing. However, an increase in ALA, PBG and other porphyrins after ketamine has been reported in a patient in the latent phase of AIP, and it would seem wise to reserve ketamine for use where haemodynamic or other considerations make it the drug of choice. The use of propofol in porphyria is also contentious to some degree. Animal data are conflicting; there is no evidence of porphyrinogenicity in the DDC-primed rat, but some evidence of induction of ALA synthetase in the chick embryo.[13] There are many case reports of patients with AIP[8,10,25,29,31,37,46,50,58] and HCP[48] and a prospective study of patients with VP[36] who received propofol safely. Although there are two reports of elevated porphyrins following propofol anaesthesia in patients with VP[59] and AIP,[16] continuous infusions of propofol were used in both cases and total doses of 900 or 1300 mg were administered; neither patient had any porphyric symptoms following the use of propofol. On balance, therefore, it appears that propofol can safely be used for induction of anaesthesia, although a question mark must remain against its use as a continuous infusion.

Inhalational agents. Nitrous oxide is well established as safe and cyclopropane and ether are also thought to be without risk. Halothane has been used in many cases of porphyria and is generally regarded as safe. There are two cases of a possible hazard attributed to halothane supported by some experimental evidence.[22] However, in view of other experimental data which do not support this view, together with extensive clinical experience of its use, halothane may be listed as safe.[22] This is particularly important as the status of the other two main potent inhalational agents, enflurane and isoflurane, is less certain. Safe use of isoflurane has been reported[5,6,29–31] and there appear to be no reports of adverse effects. Isoflurane should probably, therefore, be classified as safe, although further information needs to be obtained. Enflurane has been shown to induce porphyrin synthesis in animal models[5,43] but has been used safely in patients. There are few reports of its use, but there seems no absolute contraindication to enflurane in porphyric patients. There are no published data relating to sevoflurane or desflurane, although the short duration of action of both agents, and the minimal metabolism of the latter, make them likely to be safe. On balance, halothane would appear to be the current agent of choice, and isoflurane may be a satisfactory alternative; none of the other newer halogenated hydrocarbons are as yet absolutely contraindicated, though caution should be exercised in view of the very limited experience with their use in porphyric patients.

Neuromuscular blocking drugs. Succinylcholine has been used for many years and has been proven to be safe, as has tubocurarine. Though both pancuronium and alcuronium have been classified as unsafe by some authors, they have been widely used by many anaesthetists without harm. Atracurium[6 29 30] and vecuronium[31] have been used safely in small numbers of patients despite some experimental evidence for porphyrinogenicity. There would appear to be little to choose between these various agents; by analogy, mivacurium and rocuronium too are unlikely to prove dangerous, though there are no published data on their safety. Caution should, however, be exercised, particularly where extended use is intended, for example in the patient in the intensive care unit undergoing prolonged ventilation. As with propofol, prolonged use may not be safe, whereas a single dose may be.

Analgesic agents. Morphine and its analogues (including codeine) are of proven safety, and fentanyl has been shown to be safe both in chick embryo culture models and in clinical use. Alfentanil has also been used frequently with no reported complications. More recently, fentanyl[55] and sufentanil[54] have been used as a major component, in combination with isoflurane and atracurium, in open heart surgery without problems.[6] These cardiac surgical reports also refer to the safe use of heparin. Pethidine (meperidine) has a proven track record of safety despite a single case report implicating it in a porphyric attack.[14] Pentazocine and tilidine have been listed by several authors as unsafe, though the reasons for this are unclear. There is evidence both for[44] and against[13] the porphyrinogenicity of pentazocine in experimental systems. Of the non-opiate analgesics, aspirin, acetaminophen, indomethacin and naproxen have proven safe. Disler and Moore[14] recommend the avoidance of the pyrazalone derivatives (such as phenylbutazone), the anthranic acid derivatives (such as ibuprofen and fenoprofen) and diclofenac. There is no information regarding ketorolac.

Cardiopulmonary bypass is a specific problem, as the additional stress imposed by hypothermia, the haemolysis induced by the bypass pump, blood loss and the large number of pharmacological agents that need to be administered may all worsen the risk of development of a porphyric crisis. However, there are several reports of the safe performance of cardiac surgery in porphyric patients provided that appropriate drug regimens are selected.[49 51 54 55] Blood loss, with its consequent increase in haem demand by the bone marrow, does not appear to stress the haem synthetic pathway sufficiently to provoke a porphyric crisis.[20]

Guidelines for selecting drugs for anaesthesia in patients with porphyria

No cases of anaesthesia-induced porphyric crisis have been reported to the national porphyria referral centre at Groote Schuur Hospital in the last 20 years. This is probably not only the result of improved patient screening and careful drug selection; we believe that in many instances drugs of unproven safety or even those which are known to aggravate porphyria have been administered. The following factors are relevant, and will be taken into account by the prudent anaesthetist.

(i) There is evidence that single exposures to potent inducers, such as thiopental, are often tolerated, but that exposure in patients whose porphyria is already induced is dangerous.[40] It seems likely that the risk with modern, short-acting anaesthetic agents is low, possibly because their rapid elimination means that exposure time is not long enough for significant enzyme induction to occur. Repeated or prolonged exposure may, however, be dangerous, as may be the case with propofol described above.

(ii) There is reason to believe that exposure to multiple potential inducing agents may be far more dangerous than exposure to any one drug.

(iii) Some of the drugs traditionally listed as unsafe on the basis of animal or cell culture experiments may not, in practice, be unsafe.

(iv) Case reports reporting adverse outcomes are frequently unreliable. They may be written by clinicians inexperienced in the interpretation of porphyrin biochemical data; sometimes this amounts to blatant ignorance, as when drug outcomes are reported in patients with PCT, which is not an acute porphyria.

This has led to the more recent, lenient approach to recommendations for drug administration reflected in Table 4 and in the paragraphs above. However, a more relaxed approach is under no circumstances to be confused with a careless or unthinking approach. Every patient must be assessed individually. In particular, patients with evidence of more active porphyria or a history of acute attacks, particularly of AIP, and prolonged administration of drugs not known unequivocally to be safe, or their sequential or concomitant use, provide fertile ground for the precipitation of an attack.

Inadvertent use of porphyrinogenic drugs

If a porphyric patient is given a triggering agent, either because of failure to detect the porphyric status of the patient, or by simple human error, a number of steps have been recommended.[21] No specific prophylactic therapy is available, but since carbohydrate loading can suppress porphyrin synthesis, it is recommended that oral carbohydrate supplements should be given with a target of 200 kcal 24 h^{-1}. If oral feeding is impossible, a 10% dextrose–saline infusion should be given. Haematin, which is the most effective therapy for an acute attack, has not been evaluated as a prophylactic, but should be available and administered promptly if an attack occurs. The patient should be

Table 4 Recommendations for the use of anaesthetic drugs in the acute porphyrias (adapted from ref 24). The terms used for the recommendations are explained in Table 3, and should be read in conjunction with the text
*There are no published data on these drugs, their recommendations are based on a comparison with drugs of the same class

Drugs		Recommendation
Inhalational agents	Nitrous oxide	Use
	Cyclopropane	Use
	Halothane	Use
	Enflurane	UWC
	Isoflurane	UWC
	Sevoflurane*	UWC
	Desflurane*	UWC
Intravenous induction agents	Propofol	Use
	Ketamine	UWC
	Barbiturates	Avoid
	Etomidate	Avoid
Analgesics	Acetaminophen	Use
	Alfentanil	Use
	Aspirin	Use
	Buprenorphine	Use
	Codeine	Use
	Fentanyl	Use
	Pethidine (meperidine)	Use
	Morphine	Use
	Naloxone	Use
	Sufentanil	Use
	Diclofenac	UWECO
	Ketorolac*	UWECO
	Phenacetin	UWECO
	Tilidine	UWECO
	Pentazocine	Avoid
Neuromuscular blocking drugs	Tubocurarine	Use
	Pancuronium	Use
	Succinylcholine	Use
	Alcuronium	UWC
	Atracurium	UWC
	Rocuronium*	UWC
	Mivacurium*	UWC
	Vecuronium	UWC
Neuromuscular block reversal agents	Atropine	Use
	Glycopyrrolate	Use
	Neostigmine	Use
Local anaesthetics	Bupivacaine	Use
	Lidocaine	Use
	Prilocaine	Use
	Procaine	Use
	Tetracaine	Use
	Cocaine	UWC
	Mepivacaine	UWC
	Ropivacaine	ND/Avoid
Sedatives and anti-emetics	Domperidone	Use
	Droperidol	Use
	Phenothiazines	Use
	Temazepam	Use
	Triazolam	Use
	Benzodiazepines other than listed	UWC
	Cimetidine	UWC
	Diazepam	UWC
	Lorazepam	UWC
	Metoclopramide	UWC
	Midazolam	UWC
	Ondansetron	UWC
	Oxazepam	UWC
	Ranitidine	UWC
	Chlordiazepoxide	UWECO
	Nitrazepam	UWECO
Cardiovascular drugs	Epinephrine	Use
	Magnesium	Use
	Phentolamine	Use
	Procainamide	Use
	α-Agonists	Use
	β-Blockers	Use
	β-Agonists	Use
	Diltiazem	UWC
	Disopyramide	UWC
	Sodium nitroprusside	UWC
	Verapamil	UWC
	Hydralazine	UWECO
	Nifedipine	UWECO
	Phenoxybenzamine	UWECO

monitored carefully with urine sampling for porphyrins for at least 5 days and supportive therapy given if necessary.

Should an acute attack occur, the first step in management is to ensure that any possibly precipitating factors are withdrawn. Adequate hydration and carbohydrate intake must be ensured in the face of the nausea and vomiting which accompanies the acute attack; use of a nasogastric tube may be necessary. Pain often requires opiates in high and frequent doses. Sedation with phenothiazines may assist by encouraging sleep, which has been reported to diminish the pain, but is usually unnecessary when sufficient doses of opiate have been given. Nausea and vomiting will respond to the phenothiazines, and ondansetron may be useful if extrapyramidal side-effects occur, although its use in this setting has not been described. Beta-adrenergic blockers may be valuable in controlling tachycardia and hypertension, and may also decrease the activity of ALA synthetase. Fluid balance and electrolyte disturbances must be managed aggressively. Magnesium sulphate infusions may be useful in the management of crises associated with magnesium deficiency.[56] Should convulsions occur, the traditional anticonvulsants are, of course, largely contra-indicated, but diazepam and clonazepam may be used. Haematin is the only specific form of therapy; it is thought that it supplements the intracellular free haem pool, thus repressing ALA synthetase. This agent, together with advice on its use, is usually available from expert centres specializing in porphyria. However, it is unstable and can cause renal failure, thrombophlebitis and dose-related coagulopathy.[1 3 39] Haem arginate is more stable and does not have the adverse effects attributed to haematin.[41] It may be preferable to haematin.[57] Somatostatin decreases the rate of formation of ALA synthetase and, together with plasmapheresis, has been used successfully to reduce pain and produce complete remission of symptoms in seven porphyric patients with acute exacerbations.[33]

Conclusions

The acute porphyrias are rare but they are important in anaesthesia because of the wide range of agents that can trigger an acute crisis. The recent appearance of pharmacological agents with short half-lives and the availability of a wide range of anaesthetic drugs that are almost certainly safe in the patient with acute porphyria have markedly reduced the dangers associated with anaesthesia in these patients. Consequently, provided that reasonable precautions are adopted, and sensible guidelines followed, anaesthesia for porphyric patients should not prove unduly hazardous.

The simplest course for the practising anaesthetist to adopt is not to attempt to remember a large range of drugs that are potentially hazardous, but rather to develop a simple, safe technique based on agents that have minimal risk of triggering a porphyric crisis. On the basis of the literature reviewed in this article, it would appear that propofol is now the induction agent of choice, although ketamine may be used if required. Most muscle relaxants appear to be reasonably safe, and all of the inhalational agents, with the possible exception of enflurane, can probably be used. Analgesia can be provided with any of the opiates currently in use, though tilidine and pentazocine should be avoided and care should be taken in choosing a non-steroidal anti-inflammatory agent. Regional anaesthesia, with any of the currently available agents, is not contraindicated and may be of benefit where appropriate. There is thus a more than adequate range of pharmacological agents available for use in the porphyric patient. The choice of agent may be based more on the patient's anaesthetic and surgical requirements, rather than governed by the specific requirements imposed by porphyria.

References

1 Ashley EM. Anaesthesia for porphyria. *Br J Hosp Med* 1996; **56**: 37–42

2 Bancroft GH, Lauria JI. Ketamine induction for cesarean section in a patient with acute intermittent porphyria and achondroplastic dwarfism. *Anesthesiology* 1983; **59**: 143–4

3 Bissell DM. Treatment of acute hepatic porphyria with hematin. *J Hepatol* 1988; **6**: 1–7

4 Bohrer H, Schmidt H. Regional anesthesia as anesthetic technique of choice in acute hepatic porphyria. *J Clin Anesth* 1992; **4**: 259

5 Buzaleh AM, Enriquez de Salamanca R, Batlle AM. Porphyrinogenic properties of the anesthetic enflurane. *Gen Pharmacol* 1992; **23**: 665–69

6 Campos JH, Stein DK, Michel MK, Moyers JR. Anesthesia for aortic valve replacement in a patient with acute intermittent porphyria. *J Cardiothorac Vasc Anesth* 1991; **5**: 258–61

7 Capouet V, Dernovoi B, Azagra JS. Induction of anaesthesia with ketamine during an acute crisis of hereditary coproporphyria. *Can J Anaesth* 1987; **34**: 388–90

8 Christian AS. Safe use of propofol in a child with acute intermittent porphyria. *Anaesthesia* 1991; **46**: 423–24

9 Church SE, McColl KE, Moore MR, Youngs GR. Hypertension and renal impairment as complications of acute porphyria. *Nephrol Dialysis Transplant* 1992; **7**: 986–90

10 Cooper R. Anaesthesia for porphyria using propofol. *Anaesthesia* 1988; **43**. 611

11 De Matteis F, Aldridge WN. *Haem and Haemoproteins*, Berlin: Springer-Verlag, 1978

12 Dean G. *The Porphyrias: A Story of Inheritance and Environment*, 2nd edn. Bristol: Pitman Medical, 1971

13 Deybach JC, Da Silva V, Phung LN, Levy JC, Nordmann Y. Drug risk of hepatic porphyria. Development of an animal experiment model. *Presse Med* 1987; **16**: 68–71

14 Disler PB, Moore MR. Drug therapy in the acute porphyrias. *Clin Dermatol* 1985; **3**: 112–24

15 Eales L, Day RS, Blekkenhorst GH. The clinical and biochemical features of variegate porphyria: an analysis of 300 cases studied at Groote Schuur Hospital, Cape Town. *Int J Biochem* 1980; **12**: 837–53

16 Elcock D, Norris A. Elevated porphyrins following propofol anaesthesia in acute intermittent porphyria. *Anaesthesia* 1994; **49**: 957–58

17 Elder GH, Hift RJ, Meissner PN. The acute porphyrias. *Lancet* 1997; **349**: 1613–17

18 Famewo CE. Induction of anaesthesia with etomidate in a patient with acute intermittent porphyria. *Can Anaesth Soc J* 1985; **32**: 171–3

19 Goldberg A, Moore MR, McColl KE, Brody MJ. Porphyrin metabolism and the porphyrias. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine*, 2nd edn. Oxford: Oxford University Press, 1987; 9.136–9.145

20 Harper P, Hybinette T, Thunell S. Large phlebotomy in variegate porphyria. *J Int Med* 1997; **242**: 255–59

21 Harrison GG. Propofol anaesthesia in pharmacogenetic states. In: Rawlinson E, ed. *Focus on Infusion*. London: Current Medical Literature, 1991

22 Harrison GG, Meissner PN, Hift RJ. Anaesthesia for the porphyric patient. *Anaesthesia* 1993; **48**: 417–21

23 Harrison GG, Moore MR, Meissner PN. Porphyrinogenicity of etomidate and ketamine as continuous infusions. Screening in the DDC-primed rat model. *Br J Anaesth* 1985; **57**: 420–23

24 Hift RJ, Meissner PN, Meissner DM, Petersen LA. *Porphyria: A Guide for Patients and Doctors*. Cape Town: University of Cape Town, 1999

25 Hughes PJ. Propofol in acute porphyrias. *Anaesthesia* 1990; **45**: 415

26 Jackson S. Genetic and metabolic diseases inborn errors of metabolism. In: Katz J, Benumof J, Kadis L, eds. *Anaesthesia and Uncommon Diseases*, 3rd edn. Philadelphia: WB Saunders, 1990; 84–99

27 Jensen NF, Fiddler DS, Striepe V. Anesthetic considerations in porphyrias. *Anesth Analg* 1995; **80**: 591–9

28 Joyau M, Deybach JC, Durand M, Parmentier G, Nordmann Y. Peridural anesthesia with procaine and fentanyl in a parturient with acute intermittent porphyria. *Ann Franç Anesthes Reanimat* 1986; **5**: 453–5

29 Kantor G, Rolbin SH. Acute intermittent porphyria and caesarean delivery. *Can J Anaesth* 1992; **39**: 282–5

30 Lin YC, Chen L. Atracurium in a patient with acute intermittent porphyria. *Anesth Analg* 1990; **71**: 440–41

31 McLoughlin C. Use of propofol in a patient with porphyria. *Br J Anaesth* 1989 **62**: 114

32 McNeill MJ, Bennet A. Use of regional anaesthesia in a patient with acute porphyria. *Br J Anaesth* 1990; **64**: 371–3

33 Medenica R, Lazovic G, Long P, Corbitt W, Powell D.

Plasmapheresis combined with somatostatin is a successful treatment of porphyrias. *Ther Apher* 1997; **1**: 159–64

34 Meissner PN. Enzyme studies in variegate porphyria PhD thesis. Cape Town. University of Cape Town, 1990

35 Meissner PN, Dailey TA, Hift RJ *et al.* A R59W mutation in human protoporphyrinogen oxidase results in decreased enzyme activity and is prevalent in South Africans with variegate porphyria. *Nature Genet* 1996; **13**: 95–7

36 Meissner PN, Harrison GG, Hift RJ. Propofol as an i.v. anaesthetic induction agent in variegate porphyria. *Br J Anaesth* 1991; **66**: 60–65

37 Mitterschiffthaler G, Theiner A, Hetzel H, Fuith LC. Safe use of propofol in a patient with acute intermittent porphyria. *Br J Anaesth* 1988; **60**: 109–11

38 Moore MR, McColl KE, Rimington C, Goldberg A. *Disorders of Porphyrin Metabolism*. London: Plenum, 1987

39 Morris DL, Dudley MD, Pearson RD. Coagulopathy associated with hematin treatment for acute intermittent porphyria. *Ann Intern Med* 1981; **95**: 700–701

40 Mustajoki P, Heinonen J. General anesthesia in "inducible" porphyrias. *Anesthesiology* 1980; **53**: 15–20

41 Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. *Arch Int Med* 1993; **153**: 2004–8

42 Neilson IR, Singer MA, Marks GS. Association between the membrane-fluidizing properties and porphyrin-inducing activity of alfaxolone and related steroids. *Mol Pharmacol* 1980; **18**: 144–7

43 Parikh RK, Moore MR. Anaesthetics in porphyria: intravenous induction agents. *Br J Anaesth* 1975; **47**: 907

44 Parikh RK, Moore MR. Effect of certain anaesthetic agents on the activity of rat hepatic delta-aminolaevulinate synthase. *Br J Anaesth* 1978; **50**: 1099–103

45 Paslin DA. The porphyrias. *Int J Dermatol* 1992; **31**: 527–39

46 Rigg J, Petts V. Acute porphyria and propofol. *Anaesthesia* 1993; **48**: 1108

47 Rizk SF, Jacobson JH, Silvay G. Ketamine as an induction agent for acute intermittent porphyria. *Anesthesiology* 1977; **46**: 305–6

48 Roberts BA. 'Hereditary coproporphyria'. *Anaesth Intens Care* 1990; **18**: 138–9

49 Roby HP, Harrison GA Anaesthesia for coronary artery bypass in a patient with porphyria variegata. *Anaesth Intens Care* 1982; **10**: 276–8

50 Rushman GB, Jooste CA. Anaesthesia for the porphyric patient. *Anaesthesia* 1993; **48**: 1009

51 Shipton EA, Roelofse JA. Anaesthesia in a patient with variegate porphyria undergoing coronary bypass surgery. A case report. *S Afr Med J* 1984, **65**: 53–4

52 Silvay G, Miller R, Tausk C. Safety of ketamine in patients with acute intermittent porphyria. Case reports. *Acta Anaesthesiol Scand* 1979; **23**: 329–30

53 Slavin SA, Christoforides C. Thiopental administration in acute intermittent porphyria without adverse effect. *Anesthesiology* 1976; **44**: 77–9

54 Sneyd JR, Kreimer-Birnbaum M, Lust MR, Heflin J Use of sufentanil and atracurium anesthesia in a patient with acute porphyria undergoing coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 1995; **9**: 75–8

55 Stevens JJ, Kneeshaw JD. Mitral valve replacement in a patient with acute intermittent porphyria. *Anesth Analg* 1996, **82**: 416–18

56 Taylor RL Magnesium sulfate for AIP seizures *Neurology* 1981, **31**: 1371–2

57 Tenhunen R, Mustajoki P. Acute porphyria: treatment with heme. *Sem Liver Dis* 1998; **18**: 53–5

58 Tidmarsh MA, Baigent DF. Propofol in acute intermittent porphyria. *Br J Anaesth* 1992; **68**: 230

59 Weir PM, Hodkinson BP. Is propofol a safe agent in porphyria? *Anaesthesia* 1988; **43**: 1022–3

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ABSTRACTS

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Pulmonary hypoperfusion in cyanotic heart disease

J. A. Short*, S. Paris*, P D. Booker* and R Fletcher

Royal Liverpool Children's NHS Trust, Eaton Road, Liverpool L12 2AP, UK

In anaesthetized normal children, the arterial–endtidal $P\text{CO}_2$ difference is zero.[1] In congenital heart disease with right-to-left shunting, endtidal $P\text{CO}_2$ is less than arterial $P\text{CO}_2$, resulting in an obligatory arterial–endtidal $P\text{CO}_2$ difference, which correlates with arterial saturation.[1] However, the shunt can also reduce pulmonary blood flow, potentially causing pulmonary hypoperfusion and a further increase in the arterial–endtidal $P\text{CO}_2$ difference. We wished to see if any effect of hypoperfusion was in fact discernible, by comparing observed and predicted arterial–endtidal $P\text{CO}_2$ differences in normal and cyanotic children.

Children undergoing cardiac surgery were anaesthetized with midazolam/fentanyl/N_2O/oxygen and the lungs ventilated (Servo 900C). Recordings were made simultaneously of core temperature, haemoglobin, $S\text{a}_{\text{O}_2}$, $P\text{A}_{\text{O}_2}$, $P\text{a}_{\text{CO}_2}$, (Chiron Diagnostics 865), and $F\text{I}_{\text{O}_2}$ and $P\text{CO}_2$ (Datex Capnomac). The capnograph was calibrated against the blood gas machine daily using a calibration gas Predicted arterial–endtidal $P\text{CO}_2$ differences were calculated from the above data and from carbon dioxide dissociation curves.[1] Complete data were obtained from 60 children. However, six of the first 10 children investigated had physiologically inconsistent data; the first 10 subjects have therefore been excluded from analysis. The remaining 50 children were aged 3 days to 10 years, (median 10 months).

Figure 1 shows the observed and predicted arterial–endtidal differences, plotted against $S\text{a}_{\text{O}_2}$. The mean observed arterial–endtidal $P\text{CO}_2$ difference was 1.07 (SD 0.58) kPa; the predicted mean was 0.42 (0.29), $P<0.0001$. This suggests that most of the children studied have arterial–endtidal $P\text{CO}_2$ differences considerably greater than predicted, suggesting that pulmonary hypoperfusion is common. However, the results are at variance with previous work,[1] which demonstrated a mean arterial–endtidal $P\text{CO}_2$ difference of zero in well oxygenated children.

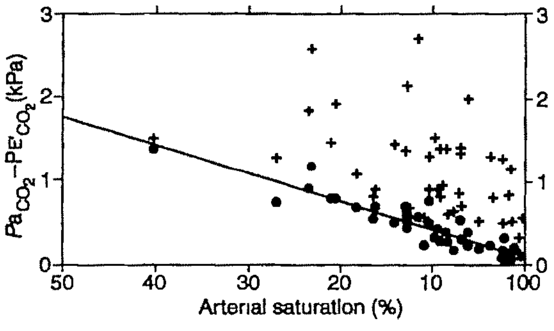

Fig 1 Observed (crosses) and predicted (dots, solid regression line) arterial–endtidal differences, plotted against $S\text{a}_{\text{O}_2}$.

Keywords: anaesthetic techniques, subarachnoid; anaesthetics local

Reference

1 Fletcher R. *Anesthesiology* 1991; **75**: 210–6

Respiratory function after removal of chest drain

A. S. Habib* and D. J. R. Duthie

University Department of Anaesthesia, Glenfield Hospital, Leicester LE3 9QP, UK

Respiratory complications are a major cause of morbidity after cardiac surgery. With trends towards earlier extubation, patients breathe spontaneously for longer with chest drains *in situ*. Hypoventilation and rapid shallow breathing initiate changes leading to atelectasis.[1] Effects of chest drains on lung function after surgery have been studied according to drain entry site and whole lung spirometry.[2] We have measured alveolar ventilation before and after chest drain removal.

Four measurements were made: before surgery (event 0), after surgery following extubation, but before (event 1), 30 min (event 2) and 4 h (event 3) after chest drains were removed. A Novametrix CO_2SMO+ was used to measure alveolar ventilation by the single breath carbon dioxide technique.[3] Data were analysed using ANOVA and linear regression analysis. $P<0.05$ was accepted as being statistically significant.

Thirteen patients were studied. They were of mean age 68 (range 54–76) yr, weight 73 (11) kg (mean (SD)) and height 171 (8) cm. Nine were male. Nine patients had coronary artery bypass grafting (CABG), two aortic valve replacement (AVR), one AVR and CABG, and one mitral valve repair and tricuspid valve replacement. Alveolar minute volumes were 6.7 (4.2) litres min^{-1} preoperatively, 3.6 (2.1) litres min^{-1} before chest drain removal and 4.0 (2.2) and 5.1 (2.8) litres min^{-1} 30 min and 4 h after chest drain removal, respectively (Fig. 2). Values at the four measurement times were significantly different ($P<0.0001$). Alveolar minute volume before chest drain removal was 3.1 (0.6–

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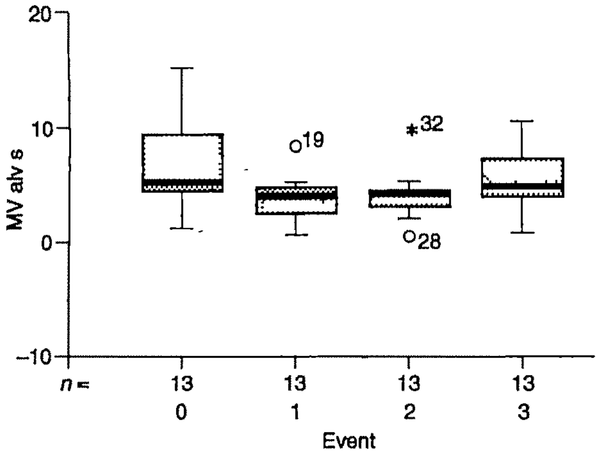

Fig 2 Alveolar minute volumes preoperatively and before and 4 h after chest drain removal (range, IQR, median, $_{\circ}19$, $_{*}32$, $_{\circ}28$ are observation outliers).

5.6) litres min^{-1} (mean (95% CL)) less than that before surgery (P=0.018). There was no increase in alveolar ventilation 30 min after chest drain removal but after 4 h, alveolar ventilation was 1.5 (0.2–2.9) litres min^{-1} higher than before chest drain removal (P=0.03). There were no differences in alveolar ventilation before surgery and 4 h after chest drain removal. There was no correlation between alveolar ventilation and time since admission to the cardiac surgery intensive care unit (r^2=0.0031).

Return to preoperative values does not occur within the first 30 min after chest drain removal.

Keywords: surgery, cardiovascular; ventilation, alveolar, lung, function

References

1 Tulla H, Takala J, Alhave E, *et al. Intensive Care Med* 1991; **17**: 365–9
2 Hagl C, Harringer W, Gohrbrandt B, Haverich A. *Chest* 1999; **115**: 757–61
3 Fletcher R, Jonson B, Cumming G, Brew J. *Br J Anaesth* 1981; **53**: 77–88

Phasic abdominal muscle action after major abdominal surgery

M. Rahman*, R. Kingshott*, W. Adams* and G. B. Drummond

Department of Anaesthetics, Royal Infirmary, Edinburgh, UK

After major abdominal surgery, episodic hypoxaemia is frequent when opioid analgesia is used. Episodes of hypoxaemia occur in association with airway obstruction. During these episodes, respiratory movements become abnormal and are associated with probable phasic abdominal muscle action.[1] Episodic respiratory disturbance and hypoxaemia are reported to occur only during sleep.[2] We studied the incidence of phasic activity of abdominal muscles in patients after major abdominal surgery, and the relationship of this activity to sleep and airway obstruction. We expected to find phasic activity and obstruction during sleep.

We recruited 12 patients about to have major surgery. We recorded EEG (C3C4 and C_zP_z), EOG, submental EMG, external oblique abdominal muscle EMG, and gas flow at the nose using a nasal cannula pressure transducer, with a miniature data logging system (Embla). Satisfactory recordings of all the signals were obtained in eight patients. The records were replayed and analysed separately by an observer who was not aware of their origin. We developed criteria for sleep staging during opioid analgesia, because the usual EEG frequencies associated with sleep did not match changes in submental EMG or EOG. These were consistent between different scorers.The appropriate trace(s) were analysed separately in 30 s epochs for phasic or continuous abdominal EMG pattern, flattening of the inspiratory flow signal and sleep state. We report median and interquartile range to summarize the data. Association between EMG, abnormal flow and sleep state was assessed by quasi likelihood in a log-linear model

Sleep occurred for 62 (46–69) % of the study time. No patient had sleep deeper than stage 2. Inspiratory flow was clear for 69 (48–81) % of the time during sleep and for 51 (28–77) % of the time during wakefulness. Abdominal muscle action was 12% more likely to be phasic during obstructed breathing in the awake state (P<0.001) and there was less phasic flow when patients were asleep. These findings are surprising and suggest that airway obstruction disrupts sleep, although there was no clear relationship between wakefulness and airway obstruction. We cannot confirm the findings of Catley and colleagues[2] that disturbed breathing is exclusively found in sleep.

Keywords: sleep; surgery

Acknowledgement

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References

1 Nimmo AF, Drummond GB. *Br J Anaesth* 1996; **77**: 317–26
2 Catley DM, Thornton C, Jordan C. *Anesthesiology* 1985; **63**: 20–8

'Target-controlled' propofol for endoscopy in snorers

P. Charters[1] and T. Jones[2]*

Departments of [1]Anaesthesia and [2]ENT, University Hospital Aintree, Liverpool L9 7AL, UK

Surgery for snoring remains controversial. Preoperative assessment is uncertain. We sought to determine whether propofol alone, delivered at minimum 'effect site' by Diprifusor TCI, would allow an appropriate endoscopic examination (i.e. close to natural sleep-induced snoring). Patients listed for snoring surgery were recruited at the preoperative surgical clinic. The majority were then admitted to a hotel adjacent to the hospital the night before surgery (for a related sleep study). The study endoscopy was the following morning and the planned surgery was in the afternoon. Obese subjects and those with obvious risk of oesophageal reflux were excluded. Approval by the local ethics committee was conditional on all sedations being personally administered by a consultant anaesthetist.

Patients fasted overnight and were not premedicated. Intravenous access was established. Patients were monitored with ECG, non-invasive arterial pressure and pulse oximetry. Respiratory rate, pattern and presence of snoring, and the degree of sedation were noted. The patients were supine; the position of their head and neck was monitored with an angle finder.[1] Supplemental oxygen was not administered. Transient dips in oxygen saturation to <90% with rapid recovery, or continuous falls to <93%, were treated by adjusting the position of the head and neck. If this failed to correct desaturation, the study was terminated. Propofol administration was increased stepwise until nasal and oral upper airway endoscopy became possible. Three schedules for initial 'effect site' increments (group 1: 0, 0.5 and 1.0 μg ml^{-1}; group 2: 0 and 1.0 μg ml^{-1}; group 3: 0 and 1.5 μg ml^{-1}) were used; all subsequent increments were 0.2 μg ml^{-1} until endoscopy or propofol discontinuation. After each increment, 5 min was allowed for equilibration before making observations and testing whether endoscopy was possible.

Table 1 Patient age, weight and height along with effect site and awakening concentration

Group	n	Age, yr	Weight, kg (SD)	Height, cm (SD)	ES, μg ml^{-1} min (SD)	Time to ES, min (SD)	AL, μg ml^{-1} (SD)	$D<20\%$
1	5	44	93.2 (16.4)	176 (5.1)	2.1 (0.1)	106.8 (20.5)	1.2 (0.3)	0
2	8	43.9	100.8 (9.8)	177.9 (7.2)	2.1 (0.2)	88.0 (11.5)	1.5 (0.4)	2
3	11	44.2	92.5 (10.1)	173.3 (6.0)	2.1 (0.3)	56.8 (20.1)	1.4 (0.5)	4

AL=awakening level; D=difference between endoscopy level and awakening level, ES=overall mean effect site

Twenty-four patients, two female, were recruited. The three groups were comparable with regard to age, weight and height (Table 1). Sedation was terminated in two patients: one (from group 2) had increasing airway difficulty and the other (group 3) had inadequate sedation (probably related to pain from a longstanding back problem.) Secretions were problematic in one patient, and in another endoscopy was limited by unsatisfactory sedation resulting from a full bladder. The overall mean effect site for endoscopic assessment was 2.1 (SD 0.4) μg ml^{-1} and the awakening level was 1.4 (SD 0.5) μg ml^{-1}. In six of the 22 patients the latter was within 20% of the endoscopy level.

Sedation by this method gave stable conditions for endoscopy (lasting up to 30 min) in 20 of 24 patients. Limited endoscopy was possible in two others. Loss of the airway occurred in one patient but was corrected rapidly on stopping the infusion. No patient complained of adverse effects 1 h after the procedure or when reviewed as ENT outpatients. Endoscopy at minimum effect site level is time consuming and analysis of the wider study of which this is a part will be needed to show how nearly this approximates to natural sleep-induced snoring.

Keywords: anaesthetics, i.v., propofol; surgery, bronchoscopy; airway

Reference

1 Horton WA, Fahy L, Charters P. *Br J Anaesth* 1989, **62** 6–12

Functional iron deficiency in critical illness

S. D. Murdoch[1], C. O'Malley[2] and M. C Bellamy[1]

[1]*Intensive Care Unit and* [2]*Department of Haematology, St James's University Hospital, Leeds, UK*

Functional iron deficiency FID is defined as >10% hypochromic red cells. It occurs commonly in critically ill patients and is associated with prolonged intensive care stay and duration of SIRS.[1] Reticulocyte haemoglobin content is also a measure of iron availability and reflects more acutely changes in iron availability to newly formed cells. Reticulocyte haemoglobin content of <28 pg represents functional iron deficiency.[2]

We studied 149 consecutive adult patients admitted to one intensive care unit. Patients were excluded if they had received a recent massive blood transfusion (>8 units) or suffered haematological malignancy or chronic renal insufficiency. Functional iron deficiency was measured using both measures: percentage red cell hypochromasia and reticulocyte haemoglobin content. Measurement was performed on routine samples (using a Bayer Advia 120 auto-analyser). The interval between sampling and testing was minimized, because red cells swell with delays in testing

Thirty-seven (25%) patients had red cell hypochromasia of >10%, in keeping with previous published results, 10 patients (7%) had functional iron deficiency as defined by reticulocyte haemoglobin content of <28 pg. There was a correlation between red cell hypochromasia and reticulocyte haemoglobin content in patients without FID by the standard definition (i.e red cell hypochromasia <10%): $r=-0.4497$; $P<0.0005$). Above this level of red cell hypochromasia ('FID' patients), there was no significant relationship between red cell hypochromasia and reticulocyte haemoglobin content ($r=0.1785$; $P=0.393$). There was no statistically significant relationship between mean corpuscular volume and percentage red cell hypochromasia for the whole population (Pearson coefficient=–0.0901; $P=0.368$). Moreover, in patients developing acute critical illness, the development of red cell hypochromasia occurs at a rate which could not be due to the production and release of new red cells alone.

Red cell hypochromasia is not diagnostic of functional iron deficiency in the critically ill patient. Functional iron deficiency as measured by reticulocyte haemoglobin content occurs less frequently in this population than has been previously reported. Red cell hypochromasia may represent an acute change in red cells, which is easily measured and warrants further investigation.

Keywords: blood, haemoglobin; intensive care

References

1 Bellamy MC, Gedney JA. *Lancet* 1998; **352**: 1903

2 Mittman N, Sreedhara R, Mushnick R, *et al. Am J Kidney Dis* 1997; **30**: 912–22

Does nitrous oxide make induction of anaesthesia with sevoflurane more exciting?

H. O'Shea*, S J Moultrie* and G B. Drummond

Department of Anaesthesia, Royal Infirmary, Edinburgh, UK

Nitrous oxide is often used as an adjunct for inhalational induction of anaesthesia with sevoflurane, but the side effects caused by nitrous oxide could make induction of anaesthesia more difficult and longer. We compared induction times, oxygenation and excitatory events during sevoflurane induction with and without nitrous oxide.

Sixty-four unpremedicated patients were recruited from elective gynaecology lists. Anaesthesia was induced with sevoflurane after random allocation to a carrier gas of either oxygen or 50% nitrous oxide in oxygen. A Mapleson D co-axial breathing circuit was used to deliver oxygen at 10 litres min^{-1} for three breaths through a well fitting face mask. Gas flow was reduced to 3 litres min^{-1} and sevoflurane 0.5% was added to the randomly allocated gas mixture. The sevoflurane concentration was doubled every three breaths to 8% then maintained for 15 s, after which the fresh gas flow was increased to 6 litres min^{-1}. These gas flow changes reduce apnoea during inhalation induction.[2]

Induction was timed from when sevoflurane was added to the carrier gas. The patient held her arm up at 30° above the horizontal during induction. Induction time was measured when the patient's arm fell to below the horizontal. We noted excitatory events such as vocalization, or movements of the head, neck, body or limbs, events when the pulse oximeter reading was <94%, and if breathing movements were absent for >10 s (apnoea). The

Table 2 Features of patients and characteristics of induction in groups receiving and not receiving nitrous oxide

	No nitrous oxide	Nitrous oxide
Number of patients	36	26
Age, yr (mean (range))	31 (16–59)	28 (16–50)
Weight, kg (mean (range))	65 (48–93)	62 (44–90)
Induction time, s (mean (SD))	102 (27)	102 (24)
No. of patients with excitation	5	10
No. of patients with Sp_{O2}<94%	2	1
No of patients with apnoea	1	0

observers were not blinded. Statistical analysis using Microsoft Excel 97 was carried out with Student's *t* test and chi-squared, as appropriate.

There were no obvious differences in the characteristics of the groups, and no statistically significant difference in induction time between the two groups. Excitation was more common in patients who received nitrous oxide ($P<0.05$) (Table 2).

In these young fit patients, adding nitrous oxide to sevoflurane for inhalation induction does not affect induction time and is associated with more excitatory movement. The use of nitrous oxide has no advantage when added to sevoflurane for inhalation induction.

Keywords: anaesthetic, gases, nitrous oxide; anaesthetics, volatile, sevoflurane; anaesthetic techniques, induction

References

1 Hall JE, Stewart JIM, Harmer M. *Anaesthesia* 1997; **52**: 410–15
2 Guracha Boru K, Drummond GB. *Br J Anaesth* 1999; **83**: 101–4

Effects of haemorrhage on the rat mesenteric microcirculation during ketamine anaesthesia

Z. L. S. Brookes, N. J. Brown* and C. S. Reilly

Division of Surgical and Anaesthetic Sciences, University of Sheffield, Sheffield, UK

We have previously performed experiments on the rat cremaster muscle during ketamine anaesthesia.[1] Following haemorrhage, a threshold systolic pressure of 105 mm Hg was observed, below which constriction of small arterioles (<30 μm) converted to dilation.[1] The aim of this study was to determine whether similar responses occurred in mesenteric vessels. Previous studies with thiopental have demonstrated differential responses to haemorrhage in the cremaster and mesenteric microcirculation.[2 3] Nineteen male Wistar rats (150–200 g) were anaesthetized with a sleep dose of ketamine (30–60 mg kg^{-1}) via the tail and maintained with an i.v. infusion of ketamine (50–90 mg kg^{-1} h^{-1}). Oxygen (30%) was blown over the animals, cardiovascular variables were monitored and the mesentery was prepared for *in vivo* microscopy.[4] FITC-BSA (0 25 ml 100 g^{-1}) was administered via the carotid artery to measure vessel integrity. An equilibration period of 30 min was allowed before the study. In all groups of animals ($n=19$), vessel diameters and macromolecular leak were recorded every 10 min for 120 min. During haemorrhage ($n=7$) and haemorrhage re-infusion ($n=6$), 10% blood volume was removed over 10 min (0.75 ml 100 g^{-1}). In the haemorrhage re-infusion group, 30 min after blood removal, saline:blood (2:1) was re-infused over 10 min.

Before haemorrhage, vessel diameters (μm) were as follows (mean (SEM), $n=13$): arterioles, 12.6 (1.1); venules, 16.2 (1.4); and capillaries, 7.5 (0.4). Initially, haemorrhage induced hypotension: systolic arterial pressure (SAP) decreased from 124.7 to 92.5 mm Hg and diastolic arterial pressure (DAP) from 92.7 to 62.7 mm Hg ($n=13$, $P<0.05$). When SAP decreased to <105 mm Hg, the percentage change in vessel diameter (mean (SEM)) demonstrated constriction of arterioles (–11.3 (2.0)%, $n=11$) and venules (–5.6 (1.4)%, $n=10$) but capillaries dilated (24.9 (6.5)%, $n=7$). However, when SAP was maintained above 105 mm Hg, arterioles (22.0%, $n=2$) and venules (10.5%, $n=3$) dilated and capillaries constricted (–7.5 (1.6)%, $n=6$). Haemorrhage had no significant effect on macromolecular leak. Re-infusion transiently improved cardiovascular variables and vessel diameter but had no effect on macromolecular leak from arterioles, venules or capillaries.

The effect of haemorrhage on the diameter of mesenteric arterioles and venules was different from that seen in the cremaster muscle during ketamine anaesthesia at the same threshold (105 mm Hg).[1] Responses also differed from those observed in the mesentery with thiopental anaesthesia,[2] suggesting that i.v. agents differentially alter microcirculatory responses to haemorrhage. Unlike with thiopental, macromolecular leak did not occur following re-infusion of ketamine,[2] so ketamine may maintain vessel integrity following haemorrhage and re-infusion.

Keywords: haemorrhage; microcirculation; anaesthetics, i.v., ketamine

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References

1 Brookes ZLS, Brown NJ, Reilly CS. *Br J Anaesth* 1998, **80**: 553P
2 Brookes ZLS, Brown NJ, Reilly CS. *Br J Anaesth* 1999; **82**: 73P–4P
3 Brookes ZLS, Reilly CS, Brown NJ. *J Vasc Res* 1998; **35**: 381
4 Kalla N. Ph.D. thesis, University of Sheffield, 1997

A new approach to noninvasive diagnosis of capillary leakage syndrome in septic shock patients

G. Marx[1]*, H. Rueckoldt[1]*, B Vangerow[1]*, M. Cobas Meyer [1]*, C. Burczyk [1]*, N. Maassen [2]*, K. F. Gratz [3]* and M. Leuwer[1]

Departments of [1]Anaesthesiology, [2]Physiology and [3]Nuclear Medicine, Hanover Medical School, D-30625 Hanover, Germany

Capillary leakage syndrome (CLS) is a frequent complication in sepsis.[1] It is characterized by loss of intravascular fluids leading to generalized oedema and haemodynamic instability despite massive fluid therapy.[2] There are no standardized criteria for diagnosis of CLS.

This prospective clinical study was performed in six patients with septic shock (SOFA score = 12 ± 2), multiple organ failure and CLS compared with six control patients. CLS was judged clinically by generalized oedema, positive fluid balance and weight gain. Fluid therapy aimed at an intrathoracic blood volume index (ITBVI) of >750 ml m^{-2}. Plasma volume measured using indocyanin green (PV-ICG), red blood cell volume measured using tagged chromium-51 (RBC-^{51}Cr) and colloid osmotic pressure (COP) were measured before (T1; 0 min) and after (T2; 90 min) administration of 300 ml of 20% albumin. Extracellular water (ECW) was determined from inulin distribution volume and bioelectrical impedance analysis.[3] Data are presented as mean (SD). Statistical comparison between groups was performed by *t*-test with Bonferroni–Holm correction. $P\leqslant0.05$ was considered significant.

These results (Table 3) suggest that ECW prediction by bioelectrical impedance in combination with measurement of COP

Table 3 Fluid compartments in CLS group compared with control group CLS=capillary leakage syndrome, PV-ICG=plasma volume measured photometrically using indocyanin green; RBC-^{51}Cr=red blood cell volume measured using erythrocytes tagged with chromium-51; COP=colloid osmotic pressure; ITBVI=intrathoracic blood volume index, Hc = central venous haematocrit, ECW-inulin=extracellular water measured by inulin distribution volume; ECW-BIA=extracellular water predicted by bioelectrical impedance (resistance at 5 kHz) *$P<0.05$ for CLS group versus control group

	T1		T2	
	CLS ($n=6$)	Control ($n=6$)	CLS ($n=6$)	Control ($n=6$)
PV-ICG (ml kg body weight^{-1})	43 (8)*	58 (10)	47 (12)	60 (9)
RBC-^{51}Cr (ml kg body weight^{-1})	20 (1)	23 (4)	21 (1)	23 (4)
COP (mm Hg)	14.3 (3.6)*	19.4 (2.5)	15.4 (3.8)*	22.2 (3.3)
Increase			1.1 (0.3)*	2.8 (1.3)
Haemoglobin (g dl^{-1})	11.7 (0.8)	11.0 (0.7)	10.6 (0.9)	10.3 (0.8)
Hc (%)	34 (2)	32 (2)	31 (2)	30 (2)
ITBVI (ml m^{-2})	775 (245)	808 (397)	761 (216)	934 (392)
ECW-inulin	40.0 (6.9)*	21.7 (3.7)		
ECW-BIA (litres)	36.7 (3.8)*	22.4 (2.8)		

response to administration of hyperoncotic solution may serve as a useful approach to diagnosis of CLS in critically ill patients.

Keywords: microcirculation, capillary; infection, septicaemia

References

1 Parrillo JE, Parker MM, Natanson C, *et al. Ann Intern Med* 1990; **113**: 227–42

2 Imm A, Carlson RW. *Crit Care Clin* 1993; **9**: 313–33.

3 Roos AN, Westendorp RG, Frolich M, *et al. Crit Care Med* 1993; **21**: 871–77

Can a 'consciousness compartment' in the brain be specified?

D. C. White and G. G Lockwood

Northwick Park Hospital, Harrow, Middlesex, UK

The site of action of anaesthetics within the brain remains elusive. We have examined available data on the rate of onset of unconsciousness in adults following vital capacity breaths of inhalational agents. This enables us to estimate the perfusion of the site of action that would be required to bring about a partial pressure equal to MAC$_{\text{awake}}$ in the measured time. We have also examined data on the time taken to recover consciousness following withdrawal of the agent.

Of the relevant publications, many relate to children and most employ nitrous oxide or other supplements which confound interpretation. The uncertainty of the solubility characteristics of the site of action makes comparison between perfusion estimates drawn from different agents unreliable. We have found only three studies[1–3] that allow comparison between their results, using the same agent (sevoflurane) and the same test as used to estimate MAC$_{\text{awake}}$ (response to command).

We have predicted alveolar concentrations during a breath-holding, vital capacity technique, assuming instantaneous mixing of inspired gas with the residual volume and no recirculation during the period of study. The rate of change of alveolar concentration is then determined by the rate of uptake of anaesthetic (a function of cardiac output and blood solubility) and the total lung capacity. This model fits the limited data available.[4] We assume that alveolar and arterial partial pressures are identical and that wash-in to the 'consciousness compartment' is exponential, with rate constant equal to the quotient of the perfusion and the blood:brain partition (taken to be 1.48 for sevoflurane) The other studies have been simulated using an updated version of our program Narkup[5], which calculates the measured end-expired concentrations accurately.

Figure 3 shows calculated perfusion rates for the mean induction and recovery times. The difference between the induction and eduction times can be explained by postulating at least two compartments essential for consciousness, having differing perfusion rates. We conclude that no single 'consciousness compartment' can be specified.

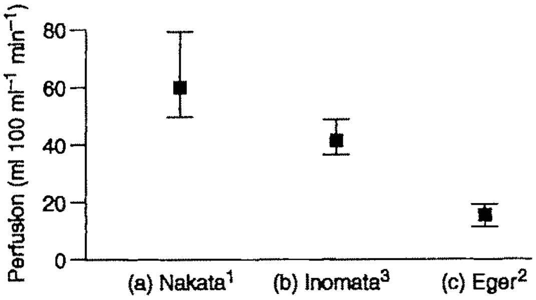

Fig 3 Calculated perfusion rates for (a, b) the mean induction times (from (a) Nakata *et al.*[1] and (b) Inomata *et al.*[3]) and (c) recovery times (from Eger *et al.*[2]). The error bars show the perfusions calculated from the 95% CI of the mean times.

Keywords: anaesthesia, depth; brain; pharmacokinetics; monitoring

References

1 Nakata Y, Goto T, Marita S. *Acta Anaesthesiol Scand* 1997, **41**: 1157–61

2 Eger EI, Gong D, Koblin DD, *et al. Anesth Analg* 1998; **86**: 414–21

3 Inomata S, Yaguchi Y, Toyooka H. *Anesth Analg* 1999; **89**: 204–8

4 Ruffles JM, Snider MT. *Anesthesiology* 1987, **67** 584–87

5 Lockwood GG, White DC. *Br J Anaesth* 1991, **66**: 519–26

Implications of twitch simulation for the mechanism of reversal of neuromuscular block

V. Nigrovic[1] and A. Amann[2]*

[1]*Departments of Anesthesiology and Pharmacology, Medical College of Ohio, Toledo, OH, USA* [2]*Department of Anaesthesia and Intensive Care Medicine, The Leopold Franzens University, Innsbruck, Austria*

The available pharmacodynamic models for nondepolarizing muscle relaxants simulate the neuromuscular block (NMB) as a function of the relaxant's concentration at the site of action. Because the reversal agents (which presumably inhibit the enzymic degradation of acetylcholine (ACh) in the synaptic cleft) do not change the concentration of relaxant and yet re-establish the full twitch strength, these models are not suitable to simulate the reversal of NMB. A promising approach would be to simulate

(i) the physiological events that occur during neuromuscular transmission and (ii) the NMB resulting from competition between ACh and the muscle relaxant for binding to postsynaptic receptors at the motor endplate. If the degradation of ACh is also explicitly included in such a model, then the presumed mechanism of action of the reversal agents may be simulated in the model. The aim of the study was to use such a model and determine whether inhibition of ACh degradation is adequate to increase a half-maximal single twitch to its full strength as has been demonstrated under clinical conditions with all the reversal agents.

The model considers explicitly the number of postsynaptic receptors (2.1×10^7) in a single endplate, the number of ACh molecules released by a stimulus (2.1×10^6), the degradation rate of free ACh ($t_{1/2}$ = 1 ms) and the affinities of the receptors for ACh and the muscle relaxant. The affinities were defined by the ratio association rate constant:dissociation rate constant. The twitch strength was defined as a function of the concentration of the 1:1 ACh–receptor complex. Events occuring after formation of the ACh–receptor complex were not considered. In the presence of IC_{50} of a hypothetical muscle relaxant, the twitch is half-maximal, while in the absence of the muscle relaxant the full strength is developed. Because the extent of acetylcholinesterase inhibition by the clinical doses of the reversal agents is not known, two conditions were simulated: mild (5%) or extensive inhibition (95%). On pharmacologic grounds, a complete inhibition of the enzyme is not plausible. The model was formulated as a set of differential equations and solved numerically using the program SCIENTIST.

The simulations indicated that a 95% inhibition of acetylcholinesterase increased the twitch from its half-maximal strength to 83%, but not to its full strength and that the peak twitch developed later and lasted much longer than in the absence of the reversal agent. To achieve the full twitch strength, the reversal agents need to triple the amount of ACh released by a stimulus.

Were the reversal agents to act exclusively by inhibiting acetylcholinesterase, the inevitable consequence would be accumulation of free ACh and receptor desensitization. If, on the other hand, the reversal agents acted by increasing the stimulus-induced release of ACh, the resulting intermittent action would be less likely to lead to receptor desensitization, but would be sufficient to re-establish the full twitch strength. Hence, the simulations indicate that the experimentally documented presynaptic action of the reversal agents may be also clinically important.

Keywords: pharmacodynamics; neuromuscular block

Influence of atracurium, cisatracurium and mivacurium on the proliferation of two human cell lines *in vitro*

F. Pühringer*, J Rieder*, M. Fleischer*, G. Hoffmann*, A Amberger*, C. Marth*, V. Nigrovic and A. Amann*

Department of Anaesthesia and Intensive Care Medicine, The Leopold Franzens University of Innsbruck, Austria

Experimental evaluation of the adverse effects of chemically reactive metabolites of atracurium generated via Hofmann elimination, that is, of acrylates, yielded contradictory results.[1–4] We decided to re-examine the question by testing the influence of atracurium and cisatracurium in two proliferating human cell lines *in vitro*: hepatoma (HEPG2) and endothelial (HUVEC) cells. For comparison, the tests also included mivacurium, a muscle relaxant from the same chemical group, which neither undergoes the elimination reaction nor produces acrylates.

The cells (2×10^4 HEPG2 and 3×10^4 HUVEC cells per well, 24 wells per plate) were incubated in Dulbecco's medium at 37°C and counted after 0, 48 and 72 h of incubation. At the start of incubation the muscle relaxants were added to the incubation medium (final concentrations: 1, 3, 10, 30 and 100 μM). In other experiments, glutathione (GSH) or *N*-acetylcysteine (NAC) was added (3 mM) to the incubation medium before the addition of atracurium or cisatracurium. The number of cells counted in four wells was averaged and expressed as per cent of the average cell count from four wells incubated without a muscle relaxant.

Atracurium and cisatracurium progressively decreased the cell proliferation in a concentration-dependent pattern, equimolar concentrations produced comparable inhibitions. After 48 and 72 h, atracurium and cisatracurium 10 μM decreased cell proliferation to ~70% in HEPG2 and to ~40% in HUVEC cells. Mivacurium did not decrease cell proliferation GSH and NAC almost completely abolished the effects of atracurium or cisatracurium.

Degradation of atracurium and cisatracurium via Hofmann elimination produces chemically reactive (electrophilic) acrylate esters that covalently react with endogenous nucleophiles The interaction may lead to a disturbance of physiological cell processes. The initial plasma concentrations of atracurium, cisatracurium and mivacurium using intubating doses (0 5, 0.15 and 0.2 mg kg^{-1}, respectively) and after dilution in plasma (volume 0.04 litre kg^{-1}) are approximately 10, 3 and 4.5 μM, respectively. Hence, even in concentrations expected clinically, atracurium and cisatracurium inhibit the proliferation of human cell lines *in vitro*. The fact that mivacurium has no such effects and that the inhibition is remedied by the nucleophilic antioxidants GSH and NAC indicates that the inhibition of cell proliferation may be ascribed to the oxidative stress of reactive metabolites

Keywords: neuromuscular block, atracurium; neuromuscular block, mivacurium; research

References

1 Reckendorfer H, *et al* *Br J Anaesth* 1992, **69**: 288–91
2 Reckendorfer H, *et al* *Br J Anaesth* 1994; **72**: 89–92
3 Sperlich M, *et al*. *Transplant Proc* 1993, **25**: 1851–2
4 Nigrovic V, *et al*. *Anesth Analg* 1986; **65**: 1107–11

Changes in cerebral oxygenation during warm (34°C) and cold (28°C) cardiopulmonary bypass using alpha and pH blood gas strategies

M. Shaaban Ali, M. Harmer*, R Vaughan*, P. Latto* and J. Dunne*

Department of Anaesthetics, UWCM, Heath Park, Cardiff CF14 4XN, UK

Imbalance between cerebral oxygen supply and demand is thought to play an important role in the development of cerebral injury during cardiac surgery with cardiopulmonary bypass (CPB) [1] The effect of CPB temperature[2] and type of acid–base strategy[3] on the brain is still controversial. The aim of this study was to compare

Table 4 Two-way ANOVA for the lowest value of S_{JO_2} during CPB for the four groups, with CPB temperature and type of pH stat as factors

	Degrees of freedom	**Lowest S_{JO_2}% during CPB**	
		F	***P***
CPB temperature	1	0 470	0 496
Type of pH stat	1	12 074	0 001
Two-way interactions (CPB temperature and type of pH)	1	0 001	0 977
Model	3	4 182	0.01

the changes in jugular bulb oxygen saturation (Sj_{O_2}) during warm and cold CPB using alpha and pH stat strategies.

Sixty patients undergoing coronary artery bypass surgery were allocated randomly into one of four equal groups (cold alpha, cold pH stat, warm alpha and warm pH stat). Sj_{O_2} samples were taken before CPB, after 5, 20 and 40 min on CPB, at the start and end of rewarming, 5 min before the end of CPB and 10 min after CPB. Intermittent antegrade warm blood cardioplegia (37°C) was used in all patients.

All groups were matched in age, number of grafts, duration of CPB and ischaemic time. The number of patients who desaturated during CPB ($Sj_{O_2}<50\%$) were five of 15 in the cold alpha group, two of 15 in the warm alpha group, one of 15 in the warm pH and none in the cold pH group. Two-way ANOVA was used to model the lowest Sj_{O_2} during CPB, with CPB temperature and blood gas management as factors (Table 4).

Significant changes in cerebral oxygenation were related only to the type of blood gas management (Table 4). The lower incidence of desaturation periods with pH stat (one in 30, compared with seven in 30) may be a result of the vasodilatory effect of increased Pa_{CO_2}.[4] The lack of significant changes in Sj_{O_2} between temperatures suggests that the penalty of prolonged rewarming[1] may safely be avoided by using a CPB temperature of ≥34°C.

Keywords: brain oxygenation; surgery, cardiovascular; temperature, body; acid–base equilibrium

Acknowledgement

We thank Emeritus Professor W W. Mapleson for statistical advice.

References

1 Croughwell ND, Newman MF, Blumenthal JA, *et al. Ann Thorac Surg* 1994, **58**: 1702–8

2 Cook DJ. *Anesth Analg* 1999; **88**: 1254–71

3 Hindman BJ. *Anesthesiology* 1998; **89**: 5–7

4 Prough DS. *Anesthesiology* 1990; **72**: 3–6

Gastric emptying following lung resection in patients receiving fentanyl–bupivacaine thoracic epidural analgesia

A. Guha*, N. Scawn*, S A Rogers*, S. H. Pennefather* and G. N Russell*

Cardiothoracic Centre NHS Trust, Thomas Drive, Liverpool L14 3PE, UK

Postoperative delays in enteral drug absorption and gastric emptying for liquids have been documented in many groups of surgical patients.[1] There is no information in the literature concerning gastric emptying in postoperative lung resection patients receiving fentanyl–bupivacaine epidural analgesia.

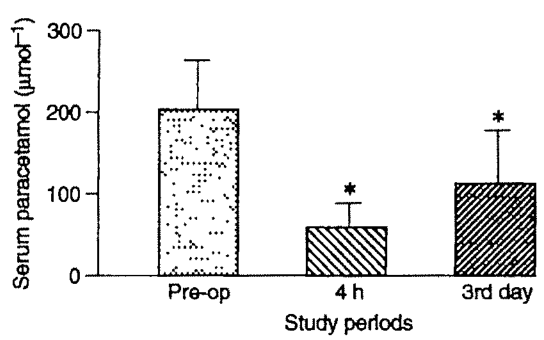

Fig 4 Maximum serum paracetamol concentrations (C_{max}) in the study periods. Data shown are mean (SD).

Eleven patients undergoing lung resection were anaesthetized by standard techniques including a thoracic epidural sited at a T4–T7 interspace and an epidural infusion of of fentanyl 10 µg ml^{-1} in 0.1% bupivacaine for intraoperative and postoperative analgesia until the end of the study. Gastric emptying was measured using a paracetamol absorption technique.[2] Patients acted as their own preoperative controls and were then assessed on the first postoperative night and again on the morning of the third day. Serial, timed blood samples were taken to measure serum paracetamol concentration. The time taken to reach a maximal concentration (t_{max}), the maximal concentration reached (C_{max}) and the total amount of paracetamol absorbed (measured by calculating the area under the paracetamol concentration time curve, AUC) were calculated. C_{max} was used as the primary measure of gastric emptying for liquids.

There was a significant decrease in C_{max} at 4 h ($P<0.0001$) and on the third day ($P<0.005$). There was a significant increase in t_{max} at 4 h ($P<0.01$). There was also a significant decrease in the total amount of paracetamol absorbed, as judged from AUC, 4 h after operation ($P<0.0001$). This persisted into the third day, and was still significant when compared with the preoperative period ($P<0.005$).

Gastric emptying has implications in clinical practice. Many of our patients undergoing thoracotomy are on long-term antianginal, antiarrhythmic and other oral medication which may need to be restarted as soon as possible. We conclude that if essential medication is to be administered to patients after lung resection with a fentanyl–bupivacaine-containing epidural infusion, careful thought needs to be given to the route of administration, as absorption of orally administered drugs may be impaired.

Keywords: analgesic, paracetamol; anaesthesia, thoracic, anaesthetic techniques, extradural

References

1 Goldhill DR, Whelpton R, Winyard JA, Wilkinson A. *Anaesthesia* 1995, **50**: 122–5

2 Hammas B, Hvarfner A, Thorn SE, Wattwil M. *Acta Anaesthesiol Scand* 1998, **42**: 102–5

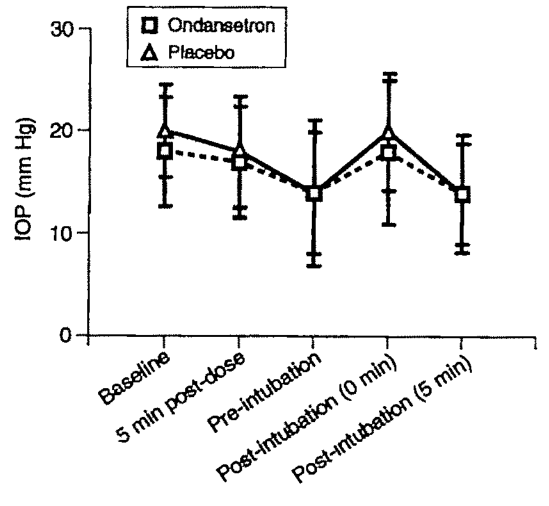

Fig 5 Change (±SD) in IOP with time with ondansetron and placebo.

Randomized prospective double-blind placebo-controlled trial of the effect of intravenous ondansetron on intra-ocular pressure during ophthalmic surgery

N. M. Robin* and S. M Mostafa

Department of Anaesthesia, Royal Liverpool University Hospital, Prescot Road, Liverpool L7 8XP, UK

Intraocular pressure (IOP) is a critical variable that needs to be controlled during ophthalmic surgery. Ondansetron has proven efficacy in the prevention and treatment of postoperative nausea and vomiting,[1] with a low side-effect profile, making it a potentially suitable choice of antiemetic in the elderly population who undergo cataract surgery. Our aim was to determine the effect of ondansetron on IOP in patients during ophthalmic surgery.

This was a double-blind placebo-controlled randomized trial. The study population comprised 40 patients undergoing elective cataract surgery under general anaesthesia. Patients were excluded if they were aged <18 yr; ASA IV or V, had vomited or received antiemetic medication in the 24 h before surgery; had a recent history of drug or alcohol abuse; were pregnant or breast feeding; had a history of glaucoma; or had a contra-indication to ondansetron. Patients were randomized into one of two groups. Following baseline IOP measurement and before anaesthesia, patients received either ondansetron 4 mg i.v. (n=20) or an equivalent volume of 0.9% saline i.v. (placebo group; n=20). IOP was recorded 5 min after injection, immediately before and after intubation and 5 min after intubation. Droperidol 0.02 mg kg^{-1} was given during surgery and rescue antiemetics were given as required postoperatively. A P-value of <0.05 was considered significant.

There were no significant differences in age or gender distribution between the ondansetron and placebo groups. The administration of ondansetron had no significant effect on IOP before or during anaesthesia (Fig. 5).

Ondansetron has no significant effect on IOP and thus can be used intravenously with confidence before induction of anaesthesia in the prophylaxis and treatment of postoperative nausea and vomiting in patients undergoing ophthalmic surgery.

Keywords: eye, intraocular pressure; vomiting, antiemetics, ondansetron

Reference

1 Figueredo ED, Canosa LG. *J Clin Anesth* 1998; **10**: 211–21

Ondansetron or prochlorperazine for antiemesis after vitreoretinal surgery?

J. M. Cupitt* and A. J. Charlton*

Manchester Royal Infirmary, Manchester, UK

Postoperative nausea and vomiting (PONV) can be as high as 50% following open eye surgery in adults[1] and can cause severe postoperative complications.[2] We compared the antiemetic effectiveness of a single dose of ondansetron with that of prochlorperazine given intraoperatively to adults undergoing vitreoretinal surgery.

We studied 154 ASA I–III patients, aged 17–88 yr, undergoing vitreoretinal surgery. All were anaesthetized using thiopentone, atracurium, morphine and isoflurane/enflurane. Patients were allocated alternately to receive either ondansetron 4 mg i.v. or prochlorperazine 12.5 mg i.m. 30 min before the end of surgery. Anaesthesia was reversed according to routine practices. The duration of preoperative fasting, duration of anaesthesia and any history of previous PONV were noted. Commencing in the recovery room, for a maximum period of 24 h (or to hospital discharge, or the successful consumption of a second postoperative meal), nursing staff asked patients standard questions concerning the occurrence of nausea, retching and vomiting, and of pain (on a 10-point scale) during the previous hour. Administration of rescue antiemetics and analgesics was recorded. We made no attempt to change anaesthesia or routine postoperative management.

There were no significant differences between the two groups in the incidence of PONV, pain scores or the use of rescue antiemetics and analgesics. The number of patients experiencing PONV was no different when assessed at either the first 6 h or the total 24 h study period. We were surprised at the overall high incidence of PONV, the high worst pain scores in the study and the relatively low incidence of administered postoperative antiemetics and analgesics, but we had chosen not to alter current postoperative routine. We conclude that ondansetron confers no benefit over prochlorperazine in preventing PONV after adult vitreoretinal surgery.

Table 5 Anaesthetic data and incidence of postoperative nausea and vomiting and pain

	Mean (range) or number	
	Ondansetron (n=75)	**Prochlorperazine** (n=79)
Time fasted (min)	620 (180–1120)	638 (135–1065)
Duration of anaesthesia (min)	130 (60–240)	127 (55–255)
Previous PONV	15	9
Nausea		
at 6 h	13	10
at 24 h	14	11
Nausea and vomiting		
at 6 h	22	20
at 24 h	30	22
Escape antiemetic	27	18
Worst pain score (number of patients)		
1–5	50	54
6–10	17	17
Rx analgesia		
oral	35	32
i.m.	6	5
oral and i.m.	10	10

Keywords: vomiting, nausea; vomiting, antiemetics, ondansetron; vomiting, antiemetics, prochlorperazine; surgery, ophthalmological

References

1 Nikki P, Pohjola S *Acta Ophthalmol* 1972, **50**: 525–31

2 Andrews PLR. *Br J Anaesth* 1992; **69** (Suppl 1): 2–19S.

Fibreoptic view through the intubating laryngeal mask compared with the laryngeal mask airway

N. McNeillis*, C. Timberlake*, M. S. Avidan, K. Sarang*, A. Choyce* and J. J. Radcliffe*

Department of Anaesthesia, King's College Hospital, London SE5 9RS, UK

The intubating laryngeal mask (ILM) was designed for blind intubation.[1] Its role as a conduit for fibreoptic intubation has yet to be established. The aim of this study was to determine how the fibreoptic view via the laryngeal mask airway (LMA) compared

Table 6 Grade of fibreoptic view via the LMA, the ILM with a tracheal tube inserted to 18 cm (ILM–tube) and the ILM without prior tube placement

	n	Grades 1 and 2	Grades 3 and 4
LMA	60	55 (91.7%)	5 (8.3%)
ILM–tube	60	31 (51.7%)	29 (48.3%)
ILM	21	18 (85.7%)	3 (14.3%)

with that via the ILM using a 'tube-first technique', as advised by the manufacturer, to lift the centrally placed epiglottic elevator bar.

This study enrolled ASA I and II patients undergoing elective surgery whose anaesthetic would normally have involved an LMA. After induction of general anaesthesia, the ILM was inserted and satisfactory ventilation was established. An 8 mm Euromedical ILM tracheal tube was inserted into the ILM to a depth of 18 cm. A 4.5 mm fibreoptic endoscope was passed through the tube to the same depth and a graded view of the laryngeal inlet was recorded. The ILM was replaced by an LMA and the fibreoptic view from the aperture bars was recorded. All views were graded using Cormack and Lehane's grading system for direct larynoscopy.[2] Interim analysis was performed during the study; it was decided to obtain an additional fibreoptic view through the ILM before tracheal tube insertion in the last 21 patients.

The view obtained through the ILM with the tube *in situ* was worse than that through the LMA ($P<0.0001$). There was no significant difference between the views through the LMA and the ILM (Table 6).

The fibreoptic view via the LMA is superior to that via the ILM using the 'tube-first technique' with the tube inserted to 18 cm. Fibreoptic endoscopy through the ILM may yield a better view of the laryngeal inlet without prior placement of a tracheal tube.

Keywords: intubation, tracheal, technique; equipment, mask anaesthesia

References

1 Brain AIJ, Verghese C, Addy EV, Kapila A *Br J Anaesth* 1997; **79**: 710–13
2 Cormack RS, Lehane J *Anaesthesia* 1984; **39**: 1105–11

A two-stage technique for insertion of a flexible laryngeal mask airway

A. Vohra

Department of Anaesthesia, Manchester Royal Infirmary, Oxford Road, Manchester, UK

The flexible laryngeal mask airway (FLMA) was first described by Alexander in 1990.[1] Its flexibility is advantageous for head and neck surgery, but also makes it difficult to insert, and many anaesthetists prefer to use the rigid version. Only two of 42 anaesthetists questioned at our institute showed a preference for the FLMA. The Bosworth introducer (Matrix Innovation Ltd, Galway, Ireland), the Portex FLMA introducer and modified stylets[2] have been described to ease insertion. This paper describes a technique which may reduce the difficulty of inserting the FLMA without the use of such aids, or fingers in the mouth (the recommended technique).

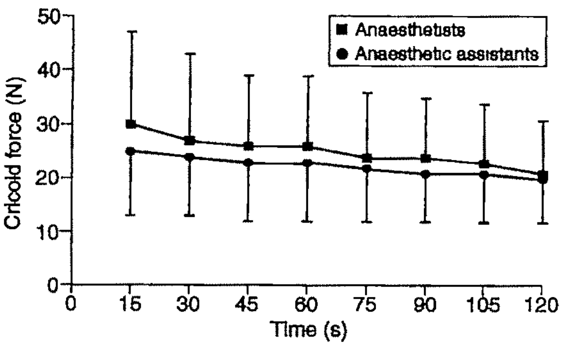

Fig 6 Cricoid force applied by anaesthetists and anaesthetic assistants.

Table 7 Insertion attempts and anaesthetist grade

Anaesthetist grade	One attempt	Two attempts	Laryngoscope	Total
SHO	109	2	3	114
Registrar	16	0	0	16
Consultant	168	2	0	170
All	293	4	3	300

The FLMA is checked and prepared in the usually recommended way and 3–5 ml of air is left in the cuff. After induction of anaesthesia, in stage 1, the head is kept in the neutral position, and the mouth is opened with a chin-lift grip using the left hand. The tube part of the FLMA is held with the other hand, close to the mask part, and all of the mask part of the FLMA is inserted into the mouth (sliding it along the roof of the mouth).

In stage 2, the left hand is moved from the patient's chin to the top of their head to extend the head into the 'sniffing the morning air' position. The tube part is then advanced into the mouth using short pushes with the right hand.

The ease of insertion of the FLMA (sizes 3–5), using this technique, was evaluated in 300 patients undergoing anaesthesia, in whom the use of an LMA was clinically appropriate. The grade of anaesthetist was recorded. Anaesthesia was induced with propofol followed by remifentanil and sevoflurane in oxygen and nitrous oxide. The FLMA was inserted when the depth of anaesthesia was adequate. A second attempt was allowed if the initial insertion was unsuccessful. If both were unsuccessful then a laryngoscope was used to aid insertion.

The patients' median (range) age was 48 (16–87) yr and median (range) weight was 75 (44–129) kg The FLMA was inserted on the first attempt in 293 (97.7%) patients, two attempts were needed in four (1.3%) patients and a laryngoscope was used in three (1%) patients (Table 7). All three (2.6%) failed attempts were performed by SHOs.

The simplicity of this method is that the mask part is inserted during stage 1 and the tube part during stage 2. We have not compared this method with another insertion technique However, we had an overall failure rate of only 1%, and 97.7% of insertions were easy.

Keywords: intubation, tracheal, technique; equipment, mask anaesthesia

References

1 Alexander CA. *Anaesthesia* 1990; **45**: 892–3
2 Philpott B, Renwick M. *Anaesthesia* 1993; **48**: 174

Failure of oral transmucosal fentanyl as a premedicant for paediatric daycase surgery

E. J. Watkins*, S. Mitchell*, V. L. Allgar* and J Brown*

Department of Anaesthesia, The General Infirmary at Leeds, Leeds LS1 3EX, UK

Pulsed dye laser ablation of portwine stains is painful and requires repeated general anaesthetics. Many children receiving

Table 8 Comparison of OTFC and placebo

	OTFC ($n=11$)	Placebo ($n=11$)	P value
Nausea in hospital, n (%)	5 (45.5%)	0 (0%)	0.03*
Vomiting in hospital, n (%)	5 (45.5%)	1 (9.1%)	0.15
Time to discharge, min (mean (SD))	112 (41.3)	60 (10.7)	<0.01*
Nausea after discharge, n (%)	3 (27.3%)	3 (27.3%)	1.00
Vomiting after discharge, n (%)	4 (36.4%)	1 (9.1%)	0.31
Pain relief after discharge (median (IQR))	1 (1–2)	2 (1–3)	0.05*

IQR, interquartile range *$P<0.05$

this treatment benefit from an anxiolytic premedication and all require good postoperative analgesia. In a randomized prospective double-blind study, we assessed the role of oral transmucosal fentanyl citrate (OTFC) in these daycases.

In this pilot study 22 children aged 3–14 yr and ASA I or II were randomly allocated to receive either a fentanyl lollipop 7–10 μg kg^{-1} followed by i.v. saline on induction, or a placebo lollipop with ketorolac 0.5 mg kg^{-1} i.v. on induction. A standard anaesthetic technique was used. Venham anxiety scores were measured both before and after the lollipop, and induction cooperation was assessed. Postoperative recovery parameters were documented, including a five-point objective pain score, and the time to discharge was noted. Patients were contacted by telephone the following day. Age and weight were compared using t-test. Other data were analysed using Mann–Whitney U-test, chi-squared and Fisher's exact tests as appropriate. $P<0.05$ was considered significant.

The Venham anxiety score[1] and induction cooperation scores were the same in both groups. Children in the OTFC group were significantly more likely to complain of nausea before discharge and also had a clinically important increase in vomiting. In the 24 h after discharge, the groups had an equal incidence of nausea but more children in the OTFC group vomited. There was a significant increase in time to discharge in the OTFC group. Children in the OTFC group reported a higher satisfaction with the pain relief provided following discharge. One patient who received OTFC required readmission for excessive sedation. Overall satisfaction was the same in both groups.

OTFC provided a marginal improvement in postoperative pain relief but with a high incidence of nausea and vomiting and a delayed discharge time (Table 8). These problems led to the termination of the study before the anticipated enrolment of 40 patients. We do not recommend the preoperative use of OTFC 7–10 μg kg^{-1} in a fully ambulatory setting.

Keywords: analgesics, opioid; analgesics, fentanyl; analgesia, postoperative; vomiting, nausea

Reference

1 Venham LL, Gaulin-Kremer E. *Paed Dentistry* 1979; **1**: 91–6

Intrapartum epidural catheter movement: a comparative study of three dressing applications

C. M. Cowan*, S. M Burns*, P. M. Barclay* and R. G. Wilkes*

Liverpool Women's Hospital, Liverpool L8 7SS, UK

The incidence of epidural catheter displacement during labour has been reported as >40%.[1] Lack of analgesia and inadvertent intravascular or subarachnoid injection are associated complications. The type of dressing may contribute to catheter migration. The object of the study was to identify the dressing method that minimized catheter migration during labour.

Based on previous data,[2] it was calculated that 35 patients per group would be required to detect a 1 cm difference in catheter movement. One hundred and thirty-five parturients were allocated randomly to receive one of three types of dressing applications following epidural catheter insertion. The length of 16 gauge Portex epidural catheter inserted into the epidural space was standardized at 4 cm. In group T, 10×25 cm Tegaderm was placed over the catheter surrounded by a 5 cm width of Mefix. In group F, 10×25 cm Tegaderm was placed over the catheter surrounded by a 5 cm width of Mefix. In addition, the in-line filter was secured to the patient's shoulder by Mefix. In group N, the catheter was secured by Niko Epi-Fix dressing surrounded by a 5 cm width of Mefix.

Table 9 Directional and absolute epidural catheter movement using three dressing methods *$P<0.01$. group N *vs* group T, †$P<0.01$: group N *vs* group F, **$P<0.05$· group N *vs* group F

	Movement, cm (median (interquartile range))		
	Group T ($n=35$)	**Group F ($n=39$)**	**Group N ($n=37$)**
MovD	0.0 (–0.5 to 1.5)	0.5 (0.0–1.0)	1.0 (0.0–2.5)*†
MovA	1.0 (0.0–2.0)	0.5 (0.0–1.5)	1.0 (0.5–2.5)**

The time when the dressing was applied, the intervertebral space used, the instrument used for skin incision and the catheter length at the skin surface were noted. When labour was complete, the time of dressing removal, integrity of dressing and catheter length at the skin surface were recorded. Catheter migration inward or outward[1] was defined as directional movement (MovD), while displacement regardless of direction was defined as absolute movement (MovA).

Results were not obtained from 24 patients. There were no differences between groups in patient characteristics, duration of labour or final dressing integrity. The catheter migrated inwards in 21 patients and outwards in 62 patients. The intervertebral space or the use of a skin incision did not significantly influence catheter displacement. Catheter movements across groups were analysed by analysis of variance and Dunnett's T3 post-test for multiple comparisons (Table 9).

We conclude that outward catheter movement is greater when a Niko Epi-Fix is used than with the other two methods. To minimize absolute catheter movement, advantage was conferred by using a Tegaderm dressing with filter fixation intead of a Niko Epi-Fix application.

Keywords: equipment, catheters, extradural; complications

References

1 Phillips DC, Macdonald R. *Anaesthesia* 1987; **42**: 661–3

2 Bishton IM, Martin PH, Vernon JM, Liu WHD. *Anaesthesia* 1992; **47**: 610–2

POSTER PRESENTATIONS

Radial arterial cannulation: topical amethocaine gel *versus* lidocaine infiltration

S. J. Olday*, R. Walpole* and J. Y. Y. Wang

Department of Anaesthetics, Royal Infirmary of Edinburgh, Edinburgh EH3 9YW, UK

Cannulation of the radial artery is painful, and our standard practice is to infiltrate 2% lidocaine before the procedure. Topical

Table 10 Summary of results. IQR, interquartile range

	Amethocaine ($n=50$)	Lidocaine ($n=50$)	P value
Cannulation time (s); median (IQR)	65 (41–142)	59 (40–105)	0.44
Failure to cannulate (n)	5	7	0.54
Additional lidocaine used (n)	7	11	0.54
Visual analogue score (0–10), median (IQR)	2 (0–4)	2 (1–3.5)	0.93
Verbal pain score (0–3), rating of			
0	15	21	0.27
1	21	17	
2	12	9	
3	2	2	

anaesthesia with EMLA cream can reduce cannulation time, improve success rate and reduce the pain of radial arterial cannulation.[1] However, amethocaine works more quickly and for longer than EMLA[2] and improves the quality of analgesia for venous cannulation.[3] For cannulation of the radial artery, its capacity to dilate vessels could be an advantage.

We recruited 100 patients about to have elective cardiac surgery. All patients were premedicated with lorazepam. They were randomized to receive either 2% lidocaine infiltration 1 min before, or topical amethocaine gel applied at least 1 h before, the attempted arterial cannulation.

We recorded the time taken to cannulate the artery successfully, and pain during the procedure (visual analogue scale completed by the patient, and a verbal pain score). We noted if additional lidocaine was used, or if the procedure took >10 min or was abandoned (classified as failure to cannulate).

To detect a difference in cannulation time of 45 s between the groups, given an estimated SD of 90 s, a sample size of 100 would give a power of 0.8. Data were analysed by Mann–Whitney U-test and chi-squared test.

The groups were similar in terms of age, gender, height, weight and operative procedure.

There was no significant difference between the groups for any variable. We conclude that topical amethocaine gel and 2% lidocaine infiltration give comparable local analgesia for radial arterial cannulation.

Keywords: anaesthetic techniques, topical; anaesthetics, local, lidocaine; arteries, cannulation

References

1 Joly L, Spaulding C, Monchi M, Ali OS, Weber S, Benhamou D. *Anesth Analg* 1998; **87**: 403–6

2 McCafferty DF, Woolfson AD, Boston V. *Br J Anaesth* 1989, **62**: 17–21

3 Lawson RA, Smart NG, Gudgeon AC, Morton NS. *Br J Anaesth* 1995; **75**: 282–5

Simulated cricoid force in paediatric anaesthesia

***S. Francis**, *S. Enani, J Shah, E. Pallett, D Rowbotham and D. Buggy

University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW, UK

Since the first description of cricoid force 40 years ago, standard teaching is to maintain a force of 44 N until the airway is secured.[1,2] In a bench model of simulated cricoid force made from plastic (PTFE), which we have previously described, we found that applied cricoid force by both anaesthetists and anaesthetic assistants was less than that recommended (30–44 N) and that most subjects were unable to maintain it for 5 min owing to fatigue.[3] There are no data to our knowledge on the cricoid force necessary to protect the airway during induction of anaesthesia in children. Our objective in this preliminary, observational study was to investigate the cricoid force that anaesthetists and anaesthetic assistants would apply to a 5-yr-old child at risk of aspiration during induction of anaesthesia, using a cricoid force simulator.

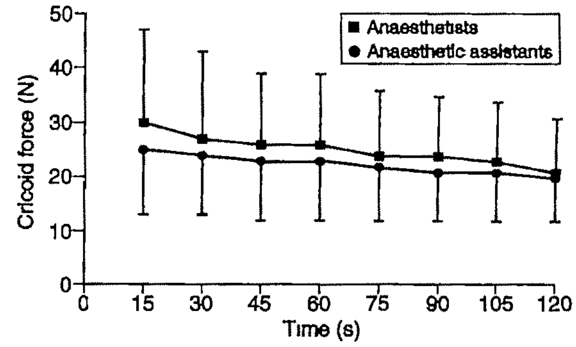

Fig 6 Cricoid force applied by anaesthetists and anaesthetic assistants

Anaesthetists of all grades ($n=45$) and anaesthetic assistants ($n=45$) were invited to apply cricoid force to the bench simulator, which was modified to take account of the smaller anatomy in children. They were asked to maintain it for 2 min, as they would in their normal practice. Participants were not permitted to view the computerized display of their applied force. Cricoid force was recorded every second for the 2 min period; the average force over 15 s intervals is reported here. Mean (SD) applied cricoid force in the two groups over the 2 min observation period is shown in Fig. 6.

Mean (SD) cricoid force applied by anaesthetists and anaesthetic assistants over the observation period was 25.1 (2.7) and 22.4 (1.7) N, respectively. Applied cricoid force decreased significantly with time in anaesthetists, but not in anaesthetic assistants.

These data indicate that in a bench model simulating applied cricoid force to a 5-yr-old child, the force applied in routine practice is of the order of 22 N. Whether this level is appropriate in paediatric practice is unknown.

Keywords: larynx, cricoid; anaesthesia, paediatric

References

1 Sellick B. *Lancet* 1961; **ii**: 404–6

2 Vanner R, Pryle BJ. *Anaesthesia* 1992; **47**: 732–5

3 Shah J, Owen-Smith O, Pallett E, Coley S, Atcheson R. *Br J Anaesth* 1998; **81**: 461P

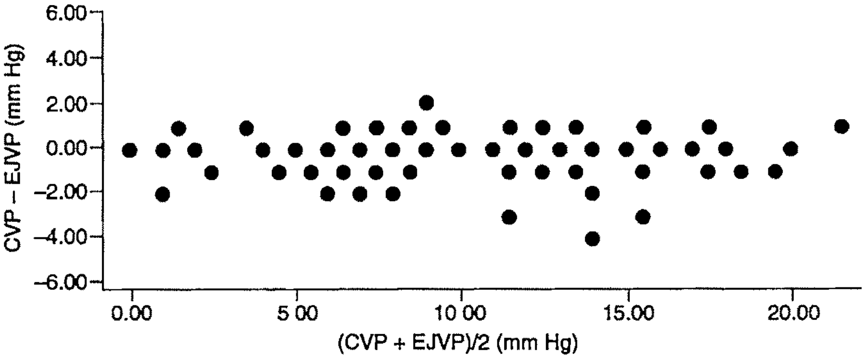

Fig 7 Bland–Altman plot comparing CVP with EJVP

Comparison of external jugular and central venous pressures in mechanically ventilated patients

J. L. Parker*, C. Flucker†, A. Maguire*, W Russell* and
J. P. Thompson

University Department of Anaesthesia, Leicester Royal Infirmary, Leicester, UK

Central venous pressure (CVP) monitoring is commonly used in theatre but catheter insertion via the internal jugular vein (IJV) is not without complications.[1] The external jugular vein (EJV) can be cannulated simply and communicates with the central venous system. Our aim was to compare EJV pressure with conventional CVP measurement in clinical practice.

Twenty patients undergoing elective major surgery requiring CVP catheter insertion were studied. After induction of anaesthesia, a triple-lumen CVP catheter was inserted via the IJV. A 20G 51 mm cannula (Abbocath, Abbot) was inserted into the EJV. The distal lumens of the CVP and external jugular catheters were connected to the same transducer via a three-way tap. For 3 h during surgery, paired measurements of mean venous pressure were taken at 30 min intervals by a blinded observer, at end-expiration and in random order. No changes in fluid therapy, inotropes, ventilation or posture were made during measurements.

. Four further patients were recruited to the study, but were excluded because of failure to cannulate the EJV. One hundred and eleven paired measurements were analysed from 20 patients (seven readings were lost because surgery finished before they could be collected and two were excluded because of a kinked EJV line). Median (range) CVP and EJV pressure (EJVP) were 8.0 (0–22) and 8.0 (0–21) mm Hg, respectively. The difference between IJV and EJV pressures was analysed by the method described by Bland and Altman[2] (Fig. 7). The mean difference between CVP and EJVP was –0.3 mm Hg (SD 1.0) with limits of agreement of –2.3 to 1.6 mm Hg (95% C.I –2.6 to 1.9 mm Hg). Previous studies using femoral venous catheters[3] [4] have accepted limits of agreement of approximately 2 mm Hg. Our results suggest that EJVP is an accurate estimate of CVP in mechanically ventilated patients. However, EJV cannulation was unsuccessful in 17% of patients approached.

Keywords: veins, venous pressure, measurement; veins, jugular

Acknowledgement

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References

1 Agee KR, Balk RA. *Crit Care Clin* 1992; **8**: 677–86
2 Bland JM, Altman DG. *Lancet* 1986, **i**: 307–10
3 Joynt GM, Gomersall CD, Buckley TA, *et al. Lancet* 1996; **347**: 1155–7
4 Kwok HM, Joynt GM, Tan P. *Crit Care Med* 1998; **26**. 461–4

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Correspondence

Placement of double lumen tubes—time to shed light on an old problem

Editor—I read the editorial by Pennefather and Russell[1] and feel that a response is in order. Although Benumof may advocate the routine use of fiberoptic bronchoscopy (FOB) for double-lumen tube (DLT) placement, that is his personal opinion and is certainly not the 'standard of care in the USA' as the authors suggest.[1] This statement has medico-legal implications and is not substantiated by any objective data. Dr Benumof and I have debated this topic for many years, and as a controversy it remains unresolved.[2 3]

I agree with Pennefather and Russell that choice of an appropriate size (large) DLT reduces the risk of misplacement. Each patient's airway dimensions can be measured directly from their chest radiograph[4 5] or CT scan[6 7] and used as an objective guide for selecting a DLT. If the dimensions of a specific DLT are known and the size of the patient's bronchus is also known, then it is possible to choose the largest tube that will safely fit that bronchus.

Why is this important? Even today, some anaesthetic textbooks erroneously recommend advancing the DLT down the airway until moderate resistance to further passage is encountered.[8] Obviously, a smaller tube in a larger airway will be advanced further if this end-point is used, increasing the chance of malposition and hypoxaemia from upper lobe obstruction. For adults (male or female), there is a highly significant correlation between depth of insertion and height.[9] For any patient who is 170 cm tall, the average depth of placement is 29 cm. For each 10 cm increase or decrease in height, the DLT is advanced or withdrawn 1.0 cm.

Pennefather and Russell give impressive statistics to support their contention that positioning problems occur frequently if a FOB is not used.[10–13] The studies they cite consider a tube to be malpositioned if it is not in *ideal* position. Ideal position is defined as when the proximal edge of the bronchial cuff is *immediately* below the tracheal carina in the appropriate bronchus. Most references do not report what size DLTs were used, and in those that did inappropriately small tubes (which presumably were advanced too far) were often chosen.[10]

A DLT can function perfectly well and still not be in ideal position.[13] What is clinically important is that the tube be in *satisfactory* position.[14] A DLT will be in satisfactory position if it is in the appropriate bronchus, if selective lung collapse and effective and safe isolation of the lungs are easily achieved, and if hypoxaemia due to tube malposition does not occur.

DLT placement in a satisfactory position can usually be achieved safely without a FOB. Pennefather and Russell quote a 40% malposition rate in a study by Cohen and colleagues,[12] but then fail to mention that there were no clinical sequeliae from tubes Cohen considered to be in poor position and that all patients with 'malpositioned DLTs had similar oxygen saturation compared to patients with well-positioned tubes'.[12]

It is probably safer for the proximal edge of the bronchial cuff to be several millimetres deep in the bronchus since there is less chance that the inflated cuff will herniate into the carina during patient positioning or from surgical manipulation. However, studies supporting the use of FOB would consider such a tube as 'malpositioned'.

Another study cited in the editorial compared traditional blind with FOB-directed placement of DLTs.[15] Those authors reported equal success (and failure) rates with both techniques. There was an 18% complication rate in over 200 patients, but the occurrence of complications *was not* correlated with the use of a FOB during intubation. When blind placement alone was used the overall incidence of complications was 16 of 119 (13%) and when a FOB was used the incidence of problems was actually higher (25 of 115, 21%)

Operator experience with any method increases the likelihood of success. FOB is just one of several adjuncts (dual capnography, spirometry, radiography) that have been used to position DLTs. Certainly, these adjuncts can be helpful and every anaesthetist who uses a DLT should be familiar with bronchoscopy for confirmation of DLT position. However, no technique is fail-safe. In my own practice and when teaching our anaesthesia residents, I do not routinely use a FOB. I believe that all anaesthetists must know how to place DLTs without an adjunct since that equipment may not always be available. As one gains more confidence and experience, there are fewer and fewer instances when a FOB is needed. I agree with Conacher and colleagues that 'clinical testing for ...DLT position remains a sound way of ensuring that placement is suitable for securing good conditions for surgery.[16]

J. B Brodsky
Department of Anesthesiology
Stanford University School of Medicine
Stanford, CA 94305, USA

1 Pennefather SH, Russell GN Placement of double lumen tubes – time to shed light on an old problem. *Br J Anaesth* 2000; **84**: 308–10
2 Benumof JL The position of a double-lumen tube should be routinely determined by fiberoptic bronchoscopy. *J Cardiothor Vasc Anesth* 1993; **7**: 513–4
3 Brodsky JB. Fiberoptic bronchoscopy should not be a standard of care when positioning double-lumen endobronchial tubes. *J Cardiothorac Vasc Anesth* 1994; **8** 373–7
4 Hannallah MS, Benumof JL, Ruttimann UE. The relationship between left mainstem bronchial diameter and patient size. *J Cardiothorac Vasc Anesth* 1995; **9**. 119–21
5 Brodsky JB, Macario A, Mark JBD. Tracheal diameter predicts double-lumen tube size: A method for selecting left double-lumen tubes. *Anesth Analg* 1996; **82**: 861–4
6 Hannallah M. Benumof JL, Silverman PM, Kelly LC, Lea D. Evaluation of an approach to choosing a left double-lumen tube size based on chest computed tomographic scan measurement of left mainstem bronchial diameter. *J Cardiothorac Vasc Anesth* 1997; **11**: 168–71
7 Chow MYH, Liam BL, Thng CH, Chong BK Predicting the size of a double-lumen endobronchial tube using computed tomographic scan measurements of the left main bronchus diameter *Anesth Analg* 1999; **88**. 302–5
8 Cohen E. Anesthetic management of one-lung ventilation. In: E. Cohen (ed.) '*The Practice of Thoracic Anesthesia*'. J.B Lippincott Co. Philadelphia, PA; 1995. p. 316
9 Brodsky JB, Benumof JL, Ehrenwerth J, Ozaki GT. Depth of placement of left double-lumen endobronchial tubes. *Anesth Analg* 1991; **73**: 570–2
10 Smith GB, Hirsch NP, Ehrenwerth J. Placement of double-lumen endobronchial tubes. Correlation between clinical impressions and bronchoscopic findings. *Br J Anaesth* 1986; **58**· 1317–20
11 Alliaume B, Coddens J, Deloof T. Reliability of auscultation in positioning of double-lumen endobronchial tubes. *Can J Anaesth* 1992; **39**: 687–90

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12 Cohen E, Neustein SM, Goldofsky S, Camunas JL. Incidence of malposition of polyvinylchloride and red rubber left-sided double-lumen tubes and clinical sequelae. *J Cardiothorac Vasc Anesth* 1995; **9**: 122–7

13 Klein U, Karzai W, Bloos F, Wohlfarth M, Gottschall R, *et al.* Role of fiberoptic bronchoscopy in conjunction with the use of double-lumen tubes for thoracic anesthesia. *Anesthesiology* 1998; **88**: 346–50

14 Brodsky JB, Macario A, Cannon WB. 'Blind' placement of plastic double-lumen tubes. *Anaesth Intensive Care* 1995, **23**: 583–6

15 Hurford WE, Alfille PH. A quality improvement study of the placement and complications of double-lumen endobronchial tubes. *J Cardiothorac Vasc Anesth* 1993, **7**: 517–20

16 Conacher ID, Herrema IH, Batchelor AM. Robertshaw double lumen tubes. a reappraisal thirty years on. *Anaesth Intensive Care* 1994; **22**: 179–83

Editor—Thank you for the opportunity to reply to Professor Brodsky. We agree that there is a need to differentiate between functionally significant and minor functionally insignificant (not ideal) double-lumen endobronchial tube (DLEBT) malplacement. We consider partial or complete occlusion of the trachea by the bronchial cuff, partial or complete occlusion of a lobar orifice (e.g. right upper lobe) and intubation of the wrong main bronchus to be functionally significant. As emphasized in our editorial Klein and colleagues[1] *did* make this distinction. During their initial fibreoptic bronchoscopy (FOB), malplacement was detected in 107 patients (53%), in 25 patients this malplacement was functionally significant (critical) despite normal findings on auscultation and inspection. After positioning the patient for surgery, a second bronchoscopy revealed critical malplacement in 48 patients.

Significant DLEBT malplacement does not always impair gas exchange. The finding by Cohen and colleagues[2] that 'patients with malpositioned tubes had similar arterial oxygen saturation to patients with well-positioned tubes' was predictable and does not weaken our argument, as implied by Brodsky. In eight of the 21 patients studied by Cohen,[2] the DLEBT was considered to be malpositioned. In three patients, all undergoing a right thoracotomy, the left DLEBT was not inserted deeply enough and the bronchial cuff partially occluded the trachea. Impaired gas exchange during one lung ventilation (OLV) would not have been expected; to the contrary, further outward displacement might improve gas exchange during 'one' lung ventilation but impair lung collapse. In a further four patients, all undergoing a left thoracotomy with a left DLEBT, the tube was inserted too deeply and the bronchial carina could not be visualized. Again impaired gas exchange during OLV would not have been expected, although difficulty re-expanding the left upper lobe after surgery could be anticipated. In the final patient, undergoing a right thoracotomy with a left DLEBT blinding inserted too deeply, impaired gas exchange during OLV could have been anticipated. It occurred; the Pa_{O_2} during OLV was 82 mm Hg whilst the patient was receiving a Fi_{O_2} of 1.0.

Brodsky states that Hurford and colleagues[3] 'compared traditional with FOB-directed placement of DLTs'. They did not. Hurford,[3] audited the *blind placement* of DLEBTs in their hospital; the choice of DLEBT used and lung to be intubated were at the discretion of the anaesthetist as was the use of a FOB to check the position of the DLEBT. When complications occurred, a FOB was used to check the position of the DLEBT and where possible ameliorate the underlying condition. To benefit patients, correct tube placement needs to be maintained. It is well recognized that tube displacement occurs during positioning for surgery and as a result of surgical manipulation and we emphasized the need for repeated bronchoscopies to maintain optimal tube position.

We agree with Brodsky that every anaesthetist who uses DLEBT should be familiar with fibreoptic bronchoscopy and that success with most techniques, including FOB, improves with experience. We would emphasize that for these skills to be of practical benefit to patients, the equipment for fibreoptic intubation not only has to be immediately available but also used.

We agree that blind placement of DLEBTs is a useful skill to acquire and we teach our specialist registrars how to place a variety of DLEBTs blindly. However, we require our registrars to check and recheck the position of blindly placed DLEBTs with a FOB; this assists in learning to blindly place DLEBTs. Most registrars need no further convincing that a FOB should be used in all patients.

Brodsky might argue that the use of a FOB during DLEBT use is not a 'standard of care' in the USA, but he cannot, in our opinion, reasonably argue that the case for the routine use of a FOB is not supported by objective data. Numerous studies have shown it is not possible to optimally place DLEBTs in all patients without a fibreoptic bronchoscope. The section of the recent national confidential enquiry into perioperative deaths[4] detailing the management of patients undergoing oesophagogastrectomy provides a salutary illustration of the potential consequences of failure to accurately place DLEBTs.

S. H Pennefather
G. N. Russell

1 Klein U, Karzai W, Bloos F, Wohlfarth M, Gottschall R, Fritz H, Gugel M, Seifert A. Role of fiberoptic bronchoscopy in conjunction with the use of double-lumen tubes for thoracic anesthesia: a prospective study. *Anesthesiology* 1998; **88**: 346–50

2 Cohen E, Neustein SM, Goldofsky S, Camunas JL. Incidence of malposition of polyvinylchloride and red rubber left-sided double-lumen tubes and clinical sequelae. *J Cardiothorac Vasc Anesth* 1995; **9**: 122–7

3 Hurford WE, Alfille PH. A quality improvement study of the placement and complications of Double-lumen endobronchial tubes. *J Cardiothorac Vasc Anesth* 1993; **7**: 517–20

4 Sherry K Management of patients undergoing oesophagectomy In: Gray AJG, Hoile RW, Ingram GS, Sherry KM, eds. *The Report of the National Confidential Enquiry into Perioperative Deaths 1996/1997.* London: The National Confidential Enquiry into Perioperative Deaths, 1998; 57–61

The Haldane effect—an explanation for increasing gastric mucosal $P\text{CO}_2$ gradients?

Editor—We read with interest the article by Jakob and colleagues demonstrating the possible influence of the Haldane effect on gastric mucosal $P\text{CO}_2$ gradients and feel that they have highlighted an important point[1] They demonstrated that in nine of 14 patients post cardiac surgery who had an increasing mucosal–arterial $P\text{CO}_2$ gradient despite an increase in total splanchnic blood flow, that this could be attributed to the decreased binding of carbon dioxide (CO_2) to haemoglobin that would accompany decreased splanchnic oxygen extraction

We believe, however, that this does not negate the use of gastric tonometry as a tool for monitoring gastric mucosal $P\text{CO}_2$. Figure 1 demonstrates the relationship between CO_2 concentration and partial pressure as first described by Christiansen–Douglas–Haldane in 1914[2] From this graph, it may be seen that it requires extreme differences in haemoglobin saturation to produce clinically significant changes in $P\text{co}_2$ (Fig. 1).

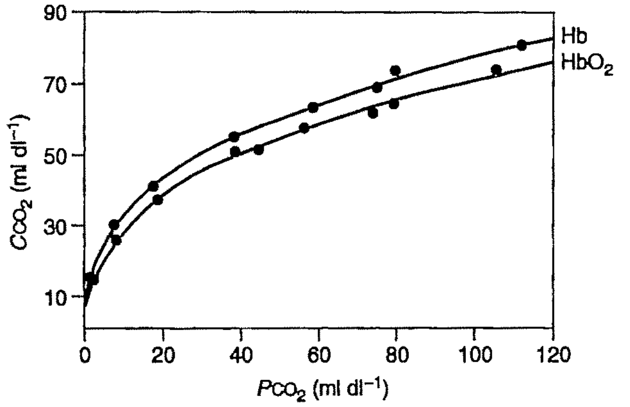

Fig 1 The CO_2 binding curves of oxyhaemoglobin (HbO_2)at 100% saturation and deoxyhaemoglobin (Hb) at 0% saturation as modified from Christiansen–Douglas–Haldane by Mertzlufft and colleagues.[5]

We should also like to comment on the effect of temperature on $P\text{co}_2$ measurements. The authors do not comment on the significant rise in core temperature seen in both patient groups during the study. It is known that temperature has an effect on carbon dioxide production, solubility and diffusion both through tissues and through the tonometer balloon, with production and diffusion decreasing and solubility increasing with decreasing temperature. Croughwell and colleagues demonstrated the effects of warm (35.5°C) and cold (30.0°C) cardiopulmonary bypass on the gastric mucosal $P\text{co}_2$ ($P\text{g}_{\text{CO}_2}$). $P\text{g}_{\text{CO}_2}$ was significantly higher with the higher temperature 4.8 kPa *vs* 5.5 kPa ($P<0.05$).[2 3] In this study by Jakob and colleagues the local gastric mucosal temperature is not known in the two groups which, given the thermogenic properties of dobutamine via its β_1-adrenoceptor activity,[4] may also contribute to the observed mucosal–arterial $P\text{co}_2$ gradient.

R Hurley
M. G Mythen
Centre of Anaesthesia
University College London Hospitals
London, UK

1 Jakob SM, Kosonen E, Ruokonen I, Parviainen I, Takala J. The Haldane Effect—an alternative explanation for increasing gastric mucosal $P\text{co}_2$ gradients? *Br J Anaesth* 1999; **83**: 740–6

2 Christiansen J, Douglas CG, Haldane JS. The absorption and dissociation of carbon dioxide by human blood. *J Physiol* 1914; **48**: 244

3 Croughwell ND, Newman MF, Lowry E, *et al* Effect of temperature during cardiopulmonary bypass on gastric mucosal perfusion. *Br J Anaesth* 1997; **78**: 34–8

4 Schiffelers SL, van Harmelen VJ, de Grauw HA, Saris WH, van Baak MA. Dobutamine as selective beta(1)-adrenoceptor agonist in in vivo studies on human thermogenesis and lipid utilization *J Appl Physiol* 1999, **87**: 977–81

5 Mertzlufft FO, Brandt L, Stanton-Hicks M, Dicks W Arterial and mixed venous blood gas status during apnoea of intubation—proof of the Christiansen–Douglas–Haldane effect in vivo. *Anaesth Intensive Care* 1989; **17**: 325–31

Editor—We read with interest the comments from Drs Hurley and Mythen concerning our article. These authors point out that only extreme changes in oxygen saturation will have a clinically significant effect on the partial carbon dioxide pressure. To demonstrate this they present the CO_2 binding curves of oxy- and deoxy-haemoglobin as originally published by Christiansen–Douglas–Haldane [1]

We showed that favourable changes in mucosal perfusion (reduction of $P\text{co}_2$ gradient in response to increased mucosal blood flow) may be missed because of the Haldane effect.[2] In contrast to Drs Hurley and Mythen, we did not discuss stationary conditions in a vascular bed, but we presented data about changes in veno–arterial and (hypothetical) mucosal–arterial CO_2 content differences. Veno–arterial CO_2 content differences are typically in the range of 10–70 ml litre^{-1} (Figs 3 and 4 in our publication[2]), whereas the CO_2 content axis in the graph that Hurley and Mythen present has a range from 0 to 900 ml litre^{-1}. Significant changes in veno–arterial or mucosal–arterial CO_2 content differences are therefore associated with only small changes in $P\text{co}_2$ gradients (Fig 4 in our publication[2]). It is important to realize that, although the amount of carbon dioxide carried in the blood by carbamino (attached to haemoglobin) is small, the difference between the amount carried in venous and arterial blood as carbamino compounds is about a third of the total arterio–venous difference.[3] This accounts for the major part of the Haldane effect.

We presented the Haldane effect under different metabolic conditions and with changes in haemoglobin and pH (Fig 5 in our publication[2]). From this figure, it is evident what different effects the same increase in blood flow may induce in the veno–arterial (or mucosal–arterial) $P\text{co}_2$ gradient. Depending on the baseline venous (or mucosal) oxygen saturation, the Haldane effect may cause a decrease or an increase in the respective $P\text{co}_2$ gradient in response to the same changes in blood flow and metabolism (Fig 5c in [2]) This clearly shows that changes in oxygen extraction have to be taken into account for the interpretation of tonometry derived variables.

The authors also comment on the effect of temperature on $P\text{co}_2$ measurements. It is true that there was a small increase in blood temperature in both study groups (0.7–0.8°C). We also reported that the splanchnic CO_2 production increased during rewarming. The effect of temperature is of importance in the interpretation of tonometry if it affects the relationship between the CO_2 content and the $P\text{co}_2$. This seems not to be the case (see below). If, as the authors propose, changes in temperature in the range of 1°C have significant effects on the solubility and diffusion of CO_2 through tissues and the tonometer balloon, tonometry should not be used in patients with changing body temperature due to, for instance, sepsis. We do not believe that this is the case. Although we do not have data on the effect of changes in temperature of less than 1°C on the diffusion of CO_2 through the tonometer balloon, the effect of such temperature change on the solubility of CO_2 at near normal body temperature is minor.[3] But if the changes in gastric mucosal $P\text{co}_2$ in the reference the authors quote[4] would be explained completely by changes in temperature, the bias in our study would be less than 0.09 kPa.

We would also like to reply to the comments from Drs De Backer, Creteur and Vincent. As the authors correctly point out, the splanchnic oxygen extraction decreased and the hepatic vein oxygen saturation increased in the patients with increasing gastric mucosal–arterial $P\text{co}_2$ gradients. The authors were also concerned about the effect of temperature on the CO_2 content. We believe that it is reasonable to assume that the changes in gastric wall temperature in these patients were comparable to the changes in blood temperature (around 0.8°C). Mainly because dissolved CO_2 content is dependent on temperature and because this content is small (1.2–1.4 mmol litre^{-1} under physiological conditions[3]), we find it hard to accept that an increase in temperature of less than 1°C should have a major impact on the results of our study. A simple calculation should underline this: according to textbooks, the arterial CO_2 content in 1 litre of blood is 480 ml (21.5 mmol) and the venous CO_2 content is 520 ml (23.3 mmol)[3], resulting in a veno–arterial CO_2 content difference of 40 ml litre^{-1} (1.8 mmol litre^{-1}). The veno–arterial difference of physically solved CO_2 is 0.17 mmol litre^{-1} or roughly 10% of the total CO_2 content difference.[3] The solubility coefficient of carbon dioxide in plasma is 0.231 mmol litre^{-1} kPa at 37°C and 0.226 mmol litre^{-1} kPa at 38°C.[3] Accordingly, the effect of increasing the blood temperature by 1°C on the veno–arterial difference of physically solved CO_2 is in the range of 2% and on the total CO_2 content difference in the range of 0.2%, hence negligible.

Drs De Backer, Creteur and Vincent suggest that some of the changes, since being within the error of the method, could have occurred by chance. We can of course not fully exclude this, but it is very unlikely, since for each patient the same analyser was always used and because we have demonstrated the same phenomenon with dopexamine in similar patients, using only the ABL blood gas analyser.[5]

Accordingly, we still believe that increases in $P\text{CO}_2$ gradient in response to increased splanchnic blood flow do occur, and the Haldane effect is a plausible explanation. Even in the very unlikely situation that the observed changes in $P\text{CO}_2$ gradient[2 5] would not be true but due to chance and methodological factors, this would not change the main message of our paper. That is, a mean increase in mucosal perfusion of almost 50% (which is certainly not in the range of one error) does not result in a decrease of gastric mucosal $P\text{CO}_2$ gradients in more than half of the patients studied, if similar changes in splanchnic and mucosal oxygen consumption and CO_2 production occurs. Hence, despite the arguments of Drs De Backer, Creteur and Vincent, we are still convinced that we have emphasized that the Haldane effect may be involved in the dissociation between mucosal–arterial $P\text{CO}_2$ gradients and total splanchnic blood flow.

S. M. Jakob
J. Takala
Kuopio
Finland

1 Christiansen J, Douglas CG, Haldane JS. The absorption and dissociation of carbon dioxide by human blood. *J Physiol* 1914; **48**: 244
2 Jakob SM, Kosonen E, Ruokonen IE, Parviainen I, Takala J. The Haldane Effect—an alternative explanation for increasing gastric mucosal $P\text{CO}_2$ gradients? *Br J Anaesth* 1999; **83**: 740–6
3 Nunn JF. *Nunn's Applied Respiratory Physiology*, 4th edn. Butterworth-Heinemann, Oxford; 1993: pp. 219–46
4 Croughwell ND, Newman MF, Lowry E, *et al.* Effect of temperature during cardiopulmonary bypass on gastric mucosal perfusion. *Br J Anaesth* 1997; **78**: 34–8
5 Uusaro A, Ruokonen E, Takala J. Gastric mucosal pH does not reflect change in splanchnic blood flow after cardiac surgery. *Br J Anaesth* 1995; **74**: 149–54

Editor—Jakob and colleagues suggest that the Haldane effect may explain a paradoxical increase in gastric mucosal $P\text{CO}_2$ (Pg_{CO_2}) secondary to an increase in mucosal blood flow. This hypothesis is attractive, but certainly difficult to prove in critically ill patients since it would require simultaneous measurements of gastric mucosal blood flow, O_2 saturation and $P\text{CO}_2$. To overcome this limitation, the authors postulated that changes in splanchnic blood flow would reflect changes in mucosal blood flow and that changes in hepatic vein O_2 saturation (ShvO_2) would reflect changes in mucosal O_2 saturation. They reported that patients with in increased gradient between Pg_{CO_2} and Pa_{CO_2} ($P\text{CO}_2$ gap) had a greater increase in ShvO_2, so that the Haldane effect was likely to apply. They also reported that the hepatic venous–arterial $P\text{CO}_2$ gradient increased in some patients while the CO_2 content differences remained unchanged.

We have several concerns and comments. First, we presume that there was an inversion between baseline and second measurement values of splanchnic O_2 saturation, since changes in oxygen extraction and saturation should go in opposite directions. Second, the patients in both groups experienced major changes in temperature and temperature was not included in the simplified formulas used to calculate CO_2 contents. Third, the measurements may be limited by technological limitations. Pg_{CO_2} was measured using two different blood gas analysers, with one analyser underestimating saline $P\text{CO}_2$, so that measurements obtained with this instrument were corrected by a correction factor calculated from a regression analysis. However, a good correlation between two methods does not imply a good agreement between the two methods.[2] A Bland and Altman[2] analysis should have been performed in order to check if measurements obtained by the two methods could be interchanged before using a correction factor for the bias. Finally, changes in Pg_{CO_2} gap were within the range of error in the measurements. The error in Pg_{CO_2} measurements are around 0.13 kPa. Creteur and colleagues[3] recently determined *in vitro* that the precision (one standard deviation) of saline tonometry is 0.26 kPa for an equilibration time of 30–60 min. Hence the error in Pg_{CO_2} should be around 0.52 (two standard deviations) and the error in $P\text{CO}_2$ gap 0.7 kPa The changes in $P\text{CO}_2$ gap here were of 0.4 kPa in group 1 and 0.6 kPa in group 2. The changes in hepatic venous $P\text{CO}_2$ gradients in patients increasing their gradients were within the range of error of these measurements (error ±0.3 kPa, changes between 0.1 and 0.3 approximately, as reported in Figure 4). Hence, the conclusions drawn from these data that the Haldane effect may be involved in the increase in Pg_{CO_2} observed in some patients are weak.

D. De Backer
J Creteur
J-L Vincent
Department of Intensive Care
Erasme University Hospital
Brussels, Belgium

1 Jakob SM, Kosonen EP, Ruokonen IE, Parviainen I, Takala J. The Haldane effect—an alternative explanation for increasing gastric mucosal $P\text{CO}_2$ gradients? *Br J Anaesth* 1999; **83**. 740–6
2 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **i**. 307–10
3 Creteur J, De Backer D, Vincent JL. Monitoring gastric mucosal carbon dioxide pressure using gas tonometry: *in vitro* and *in vivo* validation studies. *Anesthesiology* 1997; **87**· 504–10

Surgery for fractured femur and elective ICU admission at 113 yr of age

Editor—Your case report, on Surgery for fractured femur and elective ICU admission at 113 yr of age,[1] with its accompanying editorial,[2] cannot go unremarked.

The audit reported in the editorial shows that, for their case-mix, it was possible to reduce mortality to 1.5% for fractured neck of femur. The case illustrates how it might be done The nub of the argument both present is that because such results can be achieved, they ought to be. We thus appear to have reached the position that all patients, whatever their age or pre-morbidity, must be offered every available therapy, including high dependency or intensive care, if they are to be offered surgery This is odd, and feels so wrong, that it needs further analysis.

First, what feels wrong about it? You have only to look to the case report for the answer. How can be justify aggressive critical care in a wheelchair bound, confused 113 yr old, when the best possible outcome is discharge, still confused, still wheelchair bound? I cannot see any argument **for** critical care in this patient There are of course some very fit patients of great age who want and merit every effort, but many elderly patients who are fully *compos mentis* are actually just waiting to die, and would refuse intensive care. Is it reasonable to offer intensive care to someone whose best mental state is confused? When a patient is no longer mentally competent, we are required to act in their best interests, but this does not mean automatically prolonging life. 'To presume that the incompetent person must always be subjected to what many rational and intelligent persons may decline is to downgrade the status of the incompetent person by placing a lesser value on his intrinsic human worth and vitality' [3] It is clear from Bland[3] that we are not required to offer every available treatment when 'acting in the patient's best interests' If you state that surgery cannot be considered unless we offer full supporting care postoperatively, then you insist on prolonging life whatever the circumstances. That must be wrong

The mistake is, I think, to consider all operations equal, and to categorize them all as intended to cure. From this derives the idea that we should not offer surgery unless we offer the back up critical care to give the surgery a change of 'success'. But the assumption that we are always trying to cure the patient is wrong. We are not. We often undertake operations where we know that there is no chance of cure, for instance, passing an obstruction in inoperable cancer, fixing pathological fractures, etc. We anaesthetise for these procedures even though there is no chance of cure; we do not offer critical care, and we regularly leave instructions not to resuscitate. No one would criticize this.

Much surgery for fractures in the elderly is palliative. We operate to relieve acute pain, and to allow pain-free nursing care, care to pressure areas, use of bedpans, etc. Without the surgery, these procedures are painful. When the fracture is fixed, they are tolerable We do not expect all the patients to recover, but we still operate on them to make their last days more tolerable

It will be argued that it is wrong to think of operations as palliative when the patient does not have malignant disease. I would respond that many have a potential 5-yr survival which is less than those with malignant disease: very old patients do not live very long, even if 'cured' by the operation. Further, it may help to view the fall and fracture as the first events in the process of dying.

How do we decide which patients' operations are palliative, and which curative? Sometimes the answer is obvious, in either a very fit or a very unfit patient. Sometimes the answer is unclear, there is some prospect of survival, though it is not high. There, I suggest, lies the reason for operating with the patient in the best condition possible ('optimized'), but not offering critical care: those for whom the operation is palliative will select themselves, the others will survive.

I would agree with Sharrock's contention that anaesthesia and surgery by junior staff followed by return to the ward may be suboptimal, and believe consultant input may be essential. I would also agree that in some circumstances it may be inappropriate to 'optimize' before surgery, but not because, as he suggests, the medical condition will not improve until the fracture is fixed (it can often be improved, in practice), rather because when we know in advance that an operation is palliative, it may be inappropriate to optimize, as the target is not cure. I would also support NCEPOD's recommendations[4] that 'If a decision is made to operate on an elderly patient then that must include a decision to provide **appropriate** postoperative care, which **may** include high dependency or intensive care support', with the emphasis I have added: the recommendations should not be taken to mean 'critical care for all', but better and closer attention to basic care, such as fluid balance management, in appropriate cases by appropriately trained doctors.

C. P H. Heneghan
Nevin Hall Hospital
Abergaveny, UK

1 Oliver CD, White SA, Platt MW. Surgery for fractured femur and elective ICU admission at 113 yr of age. *Br J Anaesth* 2000; **84**. 260–2
2 Sharrock NE. Fractured femur in the elderly. Intensive perioperative care is warranted. *Br J Anaesth* 2000; **84**: 139–40
3 Quoted with approval by Lord Goff of Chieveley in *Airedale NHS Trust v Bland* (1993). *Med Law Rep* 1993; **4**: 39–75
4 NCEPOD (Extremes of Age. NCEPOD 1999)

Editor—I welcome Dr Heneghan's comments on this complex issue. To fully reply would involve a discussion of medical ethics, which is not my area of special interest. Nevertheless, I shall comment on three aspects.

First, is repair of a fractured neck of femur a palliative operation? Probably not in most cases, but if there is any doubt, I believe it is better to consider it a curative or corrective procedure

Secondly, should patients with confusion be treated differently? I would prefer to treat them carefully as inadequate management may add to the confusion state.

Finally, the quotes from NCEPOD appear to agree with the approach I have suggested—namely, optimize intraoperative and perioperative care. Many may benefit from a 'Step Down' or high acuity care unit for several days and some will need intensive care. My recommendation is, why not treat these patients properly if it is helpful?

N E. Sharrock
New York, USA

Editor—Death, it has often been said, is the old man's friend. Perhaps it would have best been this unfortunate lady's friend as well.[1] Certainly in my discussions with elderly patients with life-threatening conditions they fear more being left confused and dependent in a home than death itself. Reaching your 114th birthday if you cannot even tell what day it is, hardly gives cause for celebration! I am sure few will be surprised by Dr Oliver and colleagues' ability to safely administer general anaesthesia to this lady and I am unsure why this case report was accepted for publication. I have significant reservations about the advisability of intensive care admission and 31 days hospitalization for a confused old lady at the end of her life, and am concerned about the message the report may convey. Surely the issues here are analgesia and comfort care, and dignity in death? In my opinion, early fixation of hip fracture is almost always indicated, even in the most demented patient, to aid provision of adequate analgesia and nursing care. Good surgical technique and careful anaesthesia will return the vast majority of patients to the general ward in good condition; I agree with Dr Sharrock that these cases should not be left to the most junior member of the anaesthetic team.[2] Failure to tolerate surgery and anaesthesia, or the onset of complications in the postoperative period, should be considered very poor prognostic signs. The physician has special responsibility to his patients not to officiously preserve life at all costs, and to preserve their dignity now and in the future. The intensive care unit has little to offer in these situations

M J. O'Leary
New South Wales
Australia

1 Oliver CD, White SA, Platt MW. Surgery for fractured femur and elective ICU admission at 113 yr of age. *Br J Anaesth* 2000; **84**: 260–2

2 Sharrock NE. Fractured femur in the elderly. Intensive perioperative care is warranted. *Br J Anaesth* 2000; **84**: 139–40

Editor—We are grateful to those who commented about our article, as this in itself justifies its publication. The whole purpose of the report was to stimulate debate around the issues it raised and this case was one vehicle to do this—a flag waving celebration of anaesthetizing the 'oldest old' it was not. We fully acknowledge that ICU admission for this lady would have been far from appropriate given her condition on arrival in hospital. The decision should have been made at that point for limited intervention and 'death may well have proved to be a friend'. Unfortunately, many decisions are made by trainee staff, outside of standard working hours, which have major implications.

The problem and central issue is that the anaesthetists and intensivists were not party to the original treatment decision. The admitting team acknowledged the unsuitability for surgery, but then proceeded to fully resuscitate the patient. The situation was then patently different, as this lady was in pain with an unstable fracture, with perhaps months to live. We decided to proceed to surgery, being unable to find any other acceptable treatment option. It was not a sudden or easy decision and even our critics are unable to offer any better option than to commit to surgery or to do nothing.

The next issue is the method and limits of intervention. We agree with the comment that 'Good surgical technique and careful anaesthesia will return the vast majority of patients to the general ward in good condition', but which clinician can identify this 'vast majority' without error? To improve the chances of optimizing a treatment plan for any patient we must by-pass this outdated concept of anaesthesia and ICU being separate entities. Admission to ICU should not be viewed as crossing a great medical chasm; but as a continuing of treatment via operating theatres, ICU and HDU and optimization of patients before theatre is surely the way forward. ICU is an extension of quality anaesthetic care, or at least it should be

This concept should not be translated as 'to officiously preserve life at all costs', but to define treatment limitation before precipitous events force sudden moral judgements. If this patient had suffered a cardiac arrest at any time, then like Dr Heneghen we consider intervention to be inappropriate. However, if this patient had suffered postoperative respiratory failure in the recovery room, then what is the appropriate step? Extubation and death from acute dyspnoea in a recovery environment we believe is unacceptable for the patient, the relatives and the recovery staff and certainly does not 'preserve dignity'. Unplanned, emergency admission to ICU for a pre-terminal event is likewise inappropriate.

The plan for this patient was to undergo a defined 'period and level of treatment'. There was agreement that there would be no supportive measures if multi-organ failure ensued, no prolonged ventilation and no re-admission to ICU from the general ward. If critical deterioration did occur, then perhaps death with some dignity could have been achieved in a controlled environment.

We do not and never will advocate 'critical care for all', but believe that every case needs judgement on its individual merits and fully support the NCEPOD recommendations in principle, but the words 'appropriate' and 'may' do little to assist a consensus viewpoint. Dr Heneghan also highlights the other side of the debate. We often do anaesthetise patients who have no chance of 'cure' and we acknowledge that our patient overlaps into this category. We do regularly anaesthetise for 'palliative procedures', but surely not so, if we believe that they will not survive the intra-operative period? If this is the case, then the expertise of our palliative care physicians is either unavailable or under-utilized.

In summary, this report was designed to highlight the implications of early decision making as soon as a patient enters hospital and its sequelae. The treatment instigated may not be everyone's ideal, but was constructed after discussion with relatives, nursing staff, orthopaedic surgeons, anaesthetists and intensivists. A treatment plan was used, which was aimed at optimizing the 'palliative procedure' and avoiding spur-of-the-moment moral decisions. Limited ICU resource was incorporated to achieve this result and paradoxically to reverse the problems that in this case were caused by 'attention to basic care, such as fluid balance management'. At no time would we recommend the preservation of life at any cost, but consider that if a job is worth doing at all it is worth doing well.

C. D. Oliver
S. A White
London

Increasing isoflurane concentration may cause paradoxical increases in the EEG bispectral index in surgical patients

Editor—We read with interest the article by Detsch and colleagues, in which they demonstrated an increase in BIS in 39% of patients subjected to an increase in isoflurane concentrations during abdominal surgery.[1]

On closer examination of this study, it is evident that some of these patients were ASA III, and the eldest was 70 yr old. Inevitably, subjecting such a group of potentially physiologically sensitive patients to double the concentration of volatile agent necessary to maintain adequate anaesthesia, led to the frequent requirement for a norepinephrine infusion to maintain blood pressure.

The authors postulate that the increase in BIS is entirely paradoxical and that the patients' depth of anaesthesia did not lighten. The two examples the authors gave of the raw EEG traces tend to support this, although it would be necessary to see all the EEG traces to confirm it. If this is so, it must be hypothesized that intermittent EEG phenomena occurred that 'tricked' the BIS into a higher number. For this to occur there must be some increased spectral (or bispectral) power in the higher frequency bands (>30 Hz for the BetaRatio, and >40 Hz for the SynchFastSlow).[2] Irregular sudden step-changes in the EEG signal could possibly have this effect on the power spectrum. The authors comment briefly on increased alpha and beta activity and its observed frequency and yet give no data on the difference in raw EEG recordings between groups.

The alternative explanation is that the depth of anaesthesia actually did lighten. The BIS increase group not only had more patients requiring norepinephrine, but also showed a clear trend to requiring higher infusion rates Although this difference did not reach significance at the $P<0.05$ level, it did at the $P<0.1$ level (using a *t*-test). An arousal phenomenon with inotropes has been shown to occur during propofol infusions.[3] This could be either due to a direct analeptic effect by the inotrope, or a pharmacokinetic effect—an increased cardiac output causing a decrease in effective brain levels of this anaesthetic agent. Thus, the authors' statement, that a direct interaction between the norepinephrine infusion and BIS is unlikely, is unfounded and it may in fact be an important contributing factor.

The authors gave no information as to whether or not any patients (in all three groups) actually required norepinephrine before the increase in isoflurane concentration. For example, it could be that the entire BIS decrease group actually had norepinephrine prior to increasing isoflurane concentration and none of the BIS increase group did. This information should have been given clearly.

Finally, the authors question the validity of using BIS as a monitor of depth of anaesthesia during isoflurane anaesthesia. We should not lose sight of the fact that BIS is only helpful as a monitor when regarded as a single piece of the jigsaw that makes up the picture of the anaesthetized patient. If BIS merely changes from 'very deep' to 'deep' at these exaggerated doses of isoflurane then it may still be regarded as a useful tool in monitoring for awareness.

J. Andrzejowski
Sheffield, UK
J Sleigh
Hamilton, New Zealand

1 Detsch O, Schneider G, Kochs E, Hapfelmeier G, Werner C. Increasing isoflurane concentration may cause paradoxical increases in the EEG bispectral index in surgical patients. *Br J Anaesth* 2000; **84**: 33–7
2 Rampil IJ. A primer for EEG signal processing in anesthesia. *Anesthesiology* 1998; **89**: 980–1002
3 Andrzejowski J, Sleigh JW, Johnson I, Sikiotis L. Epinephrine has a stimulatory effect on the bispectral index and sedation. *Br J Anaesth* 1999; **82**: 95–6

Editor—We appreciate the comments with respect to our study[1] and share several of the considerations raised As well as the points discussed in the original manuscript, here are some additional comments on the criticisms raised in this letter Our study was prompted by the clinical observation of increases in the bispectral index (BIS) when end-tidal isoflurane concentration was increased during abdominal surgery in ASA physical status III as well as elderly patients. Considering these observations as a 'generation of hypothesis', the purpose of our study was to systematically investigate BIS responses to an increased concentration of a volatile anaesthetic rather than to investigate the mechanisms underlying variable BIS responses. Since the computation of BIS is based on a proprietary algorithm which has not yet been made public in full detail, any discussion of possible contributions of BIS sub-parameters (e.g. 'BetaRatio' or 'SynchFastSlow') to the 'paradoxical' BIS responses remains speculative.

In the letter it is postulated that an infusion of norepinephrine to support systemic haemodynamics during 1.6% isoflurane may have caused a 'direct analeptic effect' and thus, induced a decrease in the patients' anaesthetic depth. This assumption is based on a preliminary study ($n=8$) with propofol *sedation* where a bolus dose of *epinephrine* caused a BIS increase and an arousal phenomenon in six patients.[2] In contrast, we investigated deeply *anaesthetized* patients (1.6% end-tidal isoflurane) with a continuous infusion of *norepinephrine* in some patients (rather than boluses of *epinephrine*). An analeptic effect of epinephrine during sedation cannot be excluded by our study. Epinephrine may cross the blood–brain barrier resulting in an activation of cerebral metabolism.[3] Norepinephrine, in contrast, seems not to cross the intact blood–brain barrier and thus increases in cerebral metabolism occur only in the presence of a defective blood-brain barrier.[4–6] We therefore believe that it is very unlikely that norepinephrine can 'antagonize' the effects of 1.6% isoflurane.

The most compelling argument against a major contribution of norepinephrine to the paradoxical BIS responses is that 59% of patients in the 'BIS increase group' and 70% of patients in the 'BIS constant group' did not receive norepinephrine, whereas 25% of patients in the 'BIS decrease group' received norepinephrine. Likewise, we consider it unlikely that differential BIS responses were caused by norepinephrine-induced changes in the pharmacokinetics of isoflurane since we studied patients with and without norepinephrine in all groups as previously mentioned. The suggested effect of norepinephrine on isoflurane pharmacokinetics by an increase in cardiac output may play a role with anaesthetics that are delivered at a constant infusion rate (e.g. propofol). However, in our study the *end-tidal* concentration of isoflurane was maintained constant by adjusting the inspired isoflurane concentration. Thus, the discussion on the effects of changes in cardiac output on brain electrical function is purely speculative. We consider it unlikely that interactions between norepinephrine (via 'analeptic effects' or via changes in isoflurane's pharmacokinetics) and BIS responses occur. The information that no patient received norepinephrine during baseline or during recovery is presented on page 35.[1]

According to information provided by the developer of the BIS technology (Aspect Medical Systems Inc.), a BIS range from 40–60 represents 'moderate hypnotic effects' and a BIS range between 60–70 reflects 'light hypnotic effects' (see www.aspectms.com clinical user guide). The examples given in Figures 1 and 2A[1] show that in these two patients the BIS increased from 39 to 62 and from 44 to 66, respectively, during the increase in end-tidal isoflurane to 1.6%. These BIS changes would therefore relate to a change in anaesthetic depth from 'moderate' to 'light' rather than 'very deep' to 'deep' as suggested in this letter. Finally, we still question the sensitivity and specificity of BIS as a monitor of the hypnotic component of anaesthesia. It has been shown that auditory processing and memory formation is still present at BIS levels between 60 and 40.[7] In our study, BIS at baseline shows a hypnotic level that is just below this range and not – as stated in the letter – very deep. Even if BIS is used just as a single piece of the jigsaw of the anaesthetised patient's picture, this piece might obscure the picture.

O. Detsch
G. Schneider
E. Kochs
G Hapfelmeier
C Werner
Klinik fur Anaesthesiologie
Technische Universitat Munchen
Munich, Germany

1 Detsch O, Schneider G, Kochs E, Hapfelmeier G, Werner C. Increasing isoflurane concentration may cause paradoxical increases in the EEG bispectral index (BIS) in surgical patients *Br J Anaesth* 2000; **84**: 33–7
2 Andrzejowski J, Sleigh JW, Johnson I, Sikiotis L. Epinephrine has a stimulatory effect on the bispectral index and sedation. *Br J Anaesth* 1999; **82**(Supp 1): 95–6
3 King BD, Sokoloff L, Wechsler RL. The effects of l-epinephrine and l-norepinephrine upon cerebral circulation and metabolism in man *J Clin Invest* 1951; **31**. 273–9
4 MacKenzie ET, McCulloch J, O'Keane M, Pickard JD, Harper AM. Cerebral circulation and norepinephrine. Relevance of the blood–brain barrier. *Am J Physiol* 1976; **231**: 483–8
5 Berntman L, Dahlgren N, Siesjo BK. Influence of intravenously administered catecholamines on cerebral oxygen consumption and blood flow in the rat. *Acta Physiol Scand* 1978; **104**. 101–8
6 Artru AA, Nugent M, Michenfelder JD. Anesthetics affect the cerebral metabolic response to circulatory catecholamines. *J Neurochem* 1981; **36**: 1941–6
7 Lubke GH, Kerssens C, Phaf H, Sebel PS. Dependence of explicit and implicit memory on hypnotic state in trauma patients. *Anesthesiology* 1999; **90**. 670–80

Flexiblade and oral trauma

Editor—Yardeni and colleagues have described the new Flexiblade laryngoscope (Arco Medic Ltd, Omer, Israel), and suggested it may have a role in modern day anaesthesia.[1] Our department

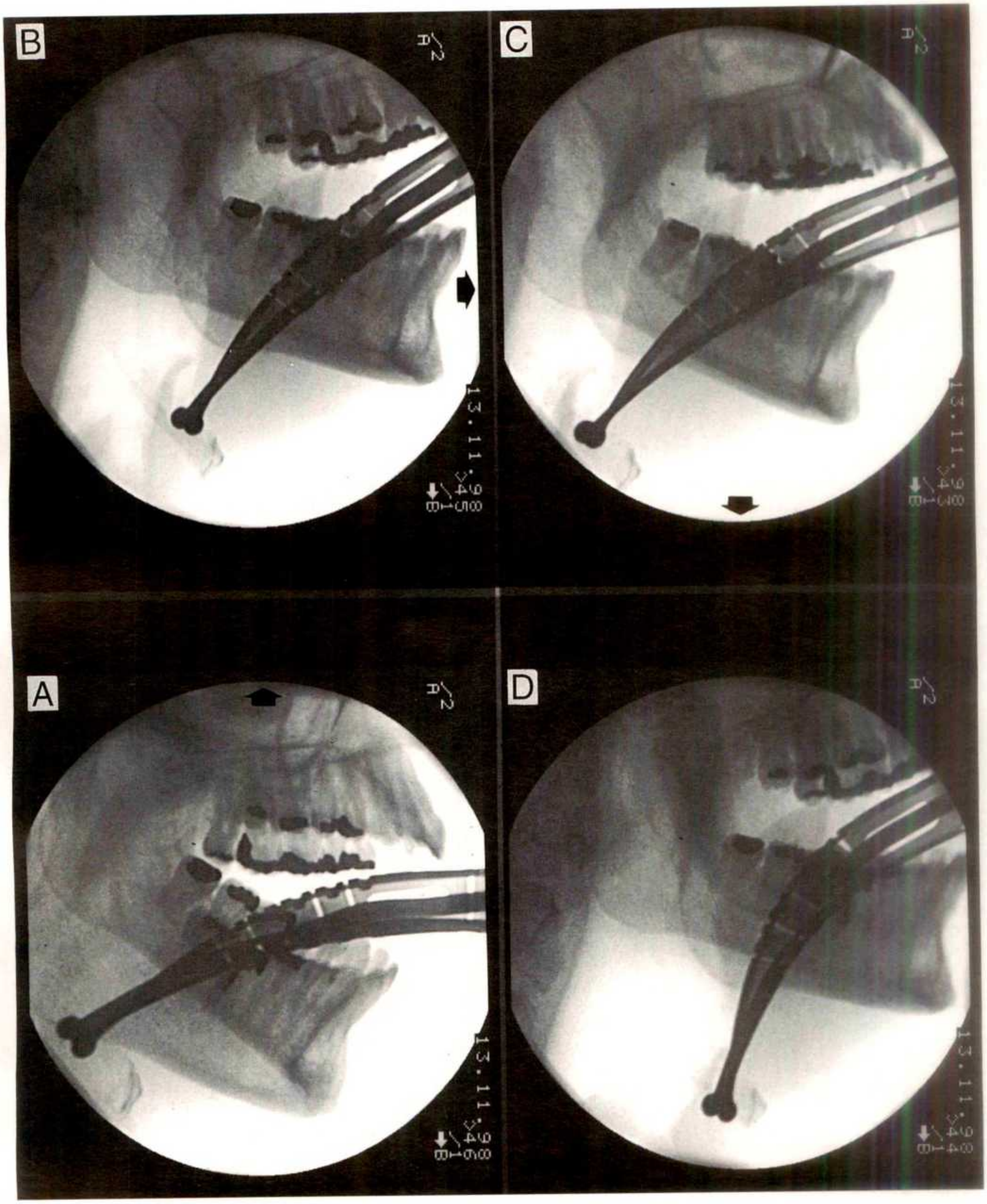

Fig 1 Sequence of x-ray radiographs of a patient with buck teeth with no damage to oral tissue.

recently tried one of these laryngoscopes and we would like to report a problem with its use. The flexibility of the Flexiblade relies on the fact that the surface of the blade is not smooth unlike other laryngoscopes. It is made up of several pieces of metal joined together. The articulations on the convex curvature of the posterior surface of the blade caused damage on insertion in the first two patients on whom we used it. In the first patient, an incisor tooth was damaged and in the second, who was edentulous, the upper gum was made to bleed. Neither of these patients had been predicted to be a difficult intubation and the Flexiblade was merely being used to ascertain its ease of use. Both patients subsequently revealed grade I views at laryngoscopy.[2] Whereas a normal Macintosh or McCoy blade would have glided over a tooth or gum, these tissues caught in the gap between the pieces of metal that make up the Flexiblade and caused damage. We could envisage this being even more likely in patients with poor mouth opening, or while manipulating the scope during a difficult intubation. We accept that we were at the beginning of a learning curve in the use of the Flexiblade, and that if we had persisted in its use, the incidence of problems might have decreased. However, there should be no learning curve as far as patient safety is concerned. We suggest that if trials show these laryngoscopes to be a useful addition to our difficult intubation trolley, that the blades are used with some sort of sheath like the Larygard (Penlon, Abingdon, England) to avoid damage to teeth or gums.

J. Andrzejowski
G. Francis
Sheffield
UK

1 Yardeni IZ, Abramowitz A, Zelman V, Katz RL. A new laryngoscope with flexible adjustable rigid blade. *Br J Anaesth* 1999; **83**: 537–9

2 Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; **39**: 1105

Editor—Thank you for giving me the opportunity to reply to Andrzejowski and Francis' letter. The Flexiblade laryngoscope was tested for nearly 2 years in the anaesthetic department of Rabin Medical Center, Petach Tikva, Israel, and for more than 1 year in the anaesthetic department of USC School of Medicine, Los Angeles, California, without reported oral trauma. There was a single case of a broken incisor tooth reported from Bickur Holim Hospital in Jerusalem, which was due to a lack of appreciation of the versatility of the blade.

The Flexiblade is inserted with its control trigger released. This permits the blade to be pulled back when encountering resistance from the tongue and the mandible. As a result, the blade changes its shape to a nearly straight one, very similar to the Miller blade. By gentle squeezing of the trigger, flexion of the intermediate portion of the blade is achieved, altering its curvature to unlimited angles, ranging from 9±1° to 30±2°.[1]

The Flexiblade is not made up of 'several pieces of metal joined together', but of one stainless steel blade, with six slots and seven windows on the flange that is subjected to a thermal treatment process to improve its flexibility.

The Flexiblade web width is not larger than that of other laryngoscope webs. At 10 cm and 12 cm distance from the tip, the web width of a size 4 standard Macintosh is 18 and 21 mm respectively. The web width of the McCoy blade is 18 and 25 mm, while the Flexiblade web is 14 and 15.5 mm only.

Dr Andrzejowski claimed that neither of his patients had been predicted to be a difficult intubation meaning that, following the Wilson classification, the mean value of the inter-incisor gap, measured with the mouth fully open, was at least 46 mm.[2] This is sufficient space to insert a nearly straight laryngoscope blade.

Insertion of any curved, rigid laryngoscope blade in a patient with a small mouth opening will invariably cause oral trauma whether the flange is smooth or not. It seems that in the reported cases the author inserted the Flexiblade while the trigger was not released. It caused the stabilization of the blade in a fixed curved position, which may disturb the smooth penetration of the blade and cause oral trauma. I can imagine that in these two cases, the mouth had not been opened as far as suggested in older and more recent texts.[3 4]

The convex curvature of the Flexiblade is not as smooth as the Macintosh blade but is well polished to prevent damage to oral tissue. Insertion of the Flexiblade with the trigger released ensures easy penetration of the blade to glide over the tongue until resting in the vallecula. This is the time to pull the trigger, without any additional levering manoeuvre. This might lengthen the blade, depress the hyoepiglottic ligament, move forward the epiglottis, depress the tongue at more than one point and reveal the tracheal inlet. This description can be seen from the sequence of x-ray radiographs of a patient with buck teeth, with no damage to the oral tissue (Fig. 1).

The suggestion of the authors to use some sort of transparent sheath to cover the blade is welcomed for both hygienic and safety reasons. I have passed a copy of the letter with the reported cases to the manufacturer to recommend the use of an elastic cover on the Flexiblade.

I. Z. Yardeni
Rabin Medical Center
Petach Tikva
Israel

1 Yardeni IZ, Abramowitz A, Zelman V, Katz RL. A new laryngoscope with flexible adjustable rigid blade. *Br J Anaesth* 1999; **83**: 537–9

2 Wilson ME, Spegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. *Br J Anaesth* 1988; **61**: 211–6

3 Bannister FB, Macbeth RG. Direct laryngoscopy and tracheal intubation. *Lancet* 1944; **2**: 651–4

4 Fell D. The practical conduct of anaesthesia. In: Aitkenhead AR, Smith G, eds. *Textbook of Anaesthesia*, 2nd edn. Churchill Livingstone 1990; 357–8

Ropivacaine 0.75% for epidural anaesthesia in a patient with severe Takayasu's disease

Editor—We read with interest the case report by Henderson and Fludder which reported an epidural anaesthetic for Caesarean section in a patient with severe Takayasu's disease.[1] The authors used an equal mixture of lidocaine 2% and bupivacaine 0.5% for epidural anaesthesia. The Caesarean section was uneventful despite a decrease in systemic blood pressure from 160 to 120 mm Hg after the first dose of local anaesthetic mixture. However, hypotension carries a high risk of syncope or severe cerebral ischaemia in these patients. We agree that the effect of pregnancy, labour, and delivery are not known to alter Takayasu's disease activity. However, a substantial number of patients have worsening of complications, particularly cardiac decompensation. We must keep in mind that Takayasu's disease is often fatal, death resulting usually from cerebral ischaemia or heart failure.[2]

We would like to solicit the authors' view on the use of ropivacaine for epidural anaesthesia in parturients with Takayasu's disease. Several studies have shown that this local anaesthetic is less cardiotoxic than bupivacaine or lidocaine.[3 4] We would like to report our experience concerning the use of ropivacaine for epidural anaesthesia in a 23-yr-old parturient with severe Takayasu's disease presenting at 28 weeks gestation and scheduled for Caesarean section for intrauterine growth retardation. The diagnosis was made 2 yr previously after an operation for abdominal aorta stenosis and upper mesenteric artery occlusion. The patient also had a history of left aortofemoral bypass and postoperative acute myocardial infarction. On admission her blood pressure was 160/110 mm Hg (usual: 130/80 mm Hg) although she was being treated with atenolol 25 mg daily. Full neurological examination revealed no signs or symptoms of disease. There was also no sign or symptom of cardiac or respiratory problems. Regional anaesthesia was provided via a lumbar epidural catheter with bolus doses of 2–3 ml of ropivacaine 0.75% every 5 min. The blood pressure was measured every 3 min After the first dose of ropivacaine, the blood pressure was 145/100 mm Hg and remained stable. Subsequent doses of ropivacaine did not alter it. Ephedrine or i.v. fluid infusion were not required. The heart rate remained stable. A total of 22 ml of ropivacaine 0.75% and sufentanil 25 μg were given over 45 min to achieve a T4 level of block. The Caesarean section was uneventful. The blood pressure decreased after delivery to 125/79 mm Hg. The postoperative course was uneventful and the patient was discharged 5 days later.

In most cases published previously, as in the paper from Henderson and Fludder,[1] hypotension was constantly reported and required the use of ephedrine and rapid i.v. fluid infusion.[1, 2] In our patient, there was haemodynamic stability throughout the case. Although there are no differences between ropivacaine and bupivacaine in terms of haemodynamic effects in healthy parturients, we think that clinical studies comparing these two drugs in patients with cardiovascular disease should be performed. Ropivacaine, which is less cardiotoxic and provides better haemodynamic stability than bupivacaine, may be of benefit for epidural anaesthesia in parturients with severe Takayasu's disease.

M. L Ousmane
M. Fleyfel
Département d'Anesthésie-Réanimation
Lille
France

1 Henderson K, Fludder P. Epidural anaesthesia for Caesarean section in a patient with severe Takayasu's disease. *Br J Anaesth* 1999; **83**: 956–9

2 Beilin Y, Bernstein H. Successful epidural anaesthesia for a patient with Takayasu's arteritis presenting for Caesarean section. *Can J Anaesth* 1993; **40**: 64–6

3 Morton CPJ, Bloomfield S, Magnusson A, Jozwiak H, McClure JH. Ropivacaine 0.75% for extradural anaesthesia in elective Caesarean section: an open clinical and pharmacokinetic study in mother and neonate. *Br J Anaesth* 1997, **79**: 3–8

4 Scott DB, Lee A, Fagan D, Bowler GMR, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with bupivacaine. *Anesth Analg* 1989; **69**: 563–9

Editor—Many thanks for the opportunity to reply to the letter by Ousmane and Fleyfel. There appears to be little difference in the outcome of patients with Takayasu's disease undergoing Caesarean section whether ropivacaine 0.75% and sufentanil is used rather than our mixture of bupivacaine 0.5% and lidocaine 2%. Indeed, the volume of local anaesthetic required was identical (and within normal limits) and the initial fall in blood pressure seen with the first dose was comparable. Moreover, the outcome for both cases was entirely uneventful to the mother and the fetus.

This should not be surprising. There is well-documented evidence in the literature that ropivacaine 0.75% compares favourably to bupivacaine 0.5% for use in epidural anaesthesia for Caesarean section.[1] It has been found to be safe and as effective as bupivacaine with a comparable onset time, sensory spread and motor block. However, Bjornestad and colleagues[2] commented that ropivacaine 0.75% was associated with a more profound drop in systolic blood pressure than bupivacaine during epidural anaesthesia for Caesarean section in otherwise fit individuals. But this has to be balanced against ropivacaine 0.75% being less cardiotoxic than bupivacaine when given in excess or inadvertently administered intravenously.[3]

Therefore the choice lies between ropivacaine with its decrease in cardiotoxicity but with the potential to cause a sustained decrease in systolic blood pressure and bupivacaine which is not as safe in excess but seems to be better at preserving perioperative blood pressure. Maintenance of blood pressure is paramount in patients with Takayasu's disease and this effect may therefore have implications for the preferred use of ropivacaine over bupivacaine. However, it is difficult to translate the effect epidural local anaesthetics have on patients with normal blood vessels to patients with one rigid and inflexible vascular tree seen with Takayasu's disease. There is some evidence from a number of published case reports[4, 5] that blood pressure generally remains unaffected during epidural anaesthesia for Caesarean section in patients with Takayasu's disease, probably as a result of the vascular fibrosis preventing vasodilatation. However, it cannot be assumed that this is likely to be the case with ropivacaine, it is my opinion that it is preferable to use bupivacaine to maintain perioperative blood pressure in patients with this disease

K. Henderson
Brighton
UK

1 Morton CP, Bloomfield S, Magnusson A, *et al.* Ropivacaine 0.75% for extradural anaesthesia in elective Caesarean section. *Br J Anaesth* 1997, **79**: 813

2 Bjornestad E, Smedvig JP, Bjerkreim T, *et al* Epidural ropivacaine 7.5 mg/ml for elective Caesarean section. a double-blind comparison of efficacy and tolerability with bupivacaine 5 mg/ml *Acta Anesthes Scandinavica* 1999; **43**. 603–8

3 Morton CP Ropivacaine: a review *Br J Hosp Med* 1997, **58**: 97–8

4 McKay RSF, Dillard SR. Management of epidural anaesthesia in a patient with Takayasu's disease. *Anesth Analg* 1992, **74**: 297–9

5 Beilin Y, Bernstein H. Successful epidural anaesthesia for a patient with Takayasu's disease presenting for Caesarean section. *Can J Anaesth* 1993; **40**: 64–6

Midazolam premedication and thiopental induction of anaesthesia

Editor—We read with interest the study by Wilder-Smith and colleagues regarding the interaction between midazolam and thiopental[1]. The authors concluded that midazolam premedication potentiates thiopental induction of anaesthesia despite being unable to demonstrate a significant difference between premedicated and unpremedicated patients for median doses required to reach specific pharmacodynamic end-points.

We recently concluded an institution-approved study whereby two groups of patients were given 50 mg boluses of thiopental at 15 s intervals for induction of anaesthesia One group ($n = 20$) received no sedative premedication or narcotic pre-induction. Another group ($n = 20$) received oral midazolam 3.75 mg, 30–120 min before induction and i.v. fentanyl 100 μg, 1 min pre-induction. The time to loss of eyelash reflex was recorded and the effect compartment concentration (C_e) was predicted using the pharmacokinetic–pharmacoydnamic (pk–pd) model described by Stanski and Maitre.[2]

We found the median effect compartment thiopental concentration at loss of the eyelash reflex to be 11.0 μg ml^{-1} in unpremedicated patients and 8.2 μg ml^{-1} in patients premedicated with midazolam. This difference was statistically significant (Mann–Whitney U-test, $P<0.05$), and the concentration ratio was 1.35. Despite the marked difference in methodology, the concentration ratio we obtained was similar to the dose ratios reported by Wilder-Smith and colleagues for loss of verbal contact and drop flex.

Using C_e to compare potency may allow direct comparison of results derived from bolus and infusion induction methods. In addition, while the injected dose can be calculated on a per unit weight basis, other covariates such as age can be incorporated in the calculation of C_e. Age has been known to influence the pharmacokinetics of hypnotics used in anaesthesia.[2 3] A lower dose in an elderly patient may result in a C_e equal to that in a young patient receiving a higher dose

While it is not possible to directly measure C_e, predicted concentrations still serve a useful purpose The C_e-response relationship can be used to devise dosing regimens which predict the response in a population.[4]

T. A. Lim
Anaesthesiology Unit
Universiti Putra
Malaysia

K Inbasegaran
Department of Anaesthesiology
Hospital Kuala Lumpur
Malaysia

1 Wilder-Smith OHG, Ravussin PA, Decosterd LA, Despland PA, Bissonnette B. Midazolam premedication and thiopental induction of anaesthesia: interactions at multiple endpoints. *Br J Anaesth* 1999; **83**: 590–5

2 Stanski DR, Maitre PO. Population pharmacokinetics and pharmacodynamics of thiopental: the effect of age revisited. *Anesthesiology* 1990; **63**: 412–22

3 Kirkpatrick T, Cockshott ID, Douglas EJ, Nimmo WS Pharmacokinetics of propofol (Diprivan) in elderly patients. *Br J Anaesth* 1988; **60**: 146–50

4 Wakeling HG, Zimmerman JB, Howell S, Glass PS. Targeting effect compartment or central compartment concentration of propofol: what predicts loss of consciousness? *Anesthesiology* 1999; **90**: 92–7

Editor—We would like to thank Lim and Inbasegaran for their interesting comment on our study of the interaction between infusion induction of anaesthesia with thiopental and midazolam premedication.[1] In this study we demonstrated significant differences in ED_{50} at various anaesthesia endpoints between premedicated and unpremedicated patients. These differences were not statistically different for median doses.

Lim and Inbasegaran suggest that the difficulties in comparing the results of drug interaction studies using either infusion or bolus models can be overcome by using pharmacokinetic–pharmacodynamic (pk–pd) modeling to calculate effect compartment concentrations, with the additional advantage that these can take into account variations due to age. In support, they cite the results of their own bolus induction study, showing significant differences in effect site concentrations between premedicated and unpremedicated patients, and resulting in a potency ratio similar to that derived from our dosage results.

We have calculated effect compartment concentrations from the results of our study using the same pk–pd model described by Stanski and Maitre.[2] For our patients, the median calculated thiopental effect site concentration at loss of verbal contact was 15.5 μg ml^{-1} (interquartile range: 9.9–18.5) for unpremedicated patients, and 12.7 μg ml^{-1} (8.9–15.9) for premedicated patients, resulting in a median effect site concentration ratio of 1.22 – close to the median dose ratio of 1.26.[1] The difference between the two median effect site concentrations is not statistically significant (Mann–Whitney *U*-test, P=0.4).

While the effect site concentration ratio in both studies is similar, median effect site concentrations in our study are 40–50% higher than those obtained by Lim and Inbasegaran. The difference in concentrations may in part be explained by the addition of i.v. fentanyl to midazolam premedication by Lim and Inbasegaran. It may also be due to methodological differences either in endpoint determination, i.e. loss of eye-lash reflex *vs* loss of verbal contact, or in study design, i.e. waiting for the endpoint to occur after giving a bolus *vs* determining it during continuous infusion. These differences will continue to need to be taken into account in comparing drug interaction studies. The technique of using predicted effect site concentrations to make the results of different drug interaction models comparable warrants further investigation and deserves to be included in future studies.

O. H G Wilder-Smith
Nociception Research Group
Bern University
Switzerland

1 Wilder-Smith OHG, Ravussin PA, Decosterd LA, Despland PA, Bissonnette B. Midazolam premedication and thiopental induction of anaesthesia: interactions at multiple endpoints. *Br J Anaesth* 1999; **83**: 590–5

2 Stanski DR, Maitre PO. Population pharmacokinetics and pharmacodynamics of thiopental: the effect of age revisited. *Anesthesiology* 1990; **63**: 412–22

Patient-controlled analgesia in labour

Editor—The article by Thurlow and Waterhouse on the use of remifentanil patient-controlled analgesia (PCA) in parturients with contraindications to the use of epidural analgesia in labour, was interesting.[1] Remifentanil is being used extensively in general anaesthetics, and this opens up a new application for its use as an effective analgesic modality during labour. I would like to add some further information pertaining to this rapidly developing area of clinical practice.

The use of an arbitrary figure (platelet count <100 000 mm^{-3}) as a contraindication to epidural analgesia in labour is questionable. Belin and co-workers report the largest series of parturients who had an epidural anaesthetic placed without complications when the platelet count was <100 000 mm^{-3}.[2] None of their patients had any clinical evidence of bleeding or decreasing platelet count at the time of epidural catheter placement. They recommend that a patient's entire clinical presentation be taken into account when deciding on the appropriate anaesthetic technique.

Based on a recent survey, most anaesthetists (66% of those in academic practice and 55% of those in private practice) will place an epidural anaesthetic when the platelet count is between 80 000 and 100 000 mm^{-3}.[3]

While the authors mention the use of pethidine and fentanyl PCA techniques during labour, butorphanol tartrate, an analgesic possessing mixed agonist-antagonist activity at opiate receptors, also has a use in intravenous PCA in parturients prone to drug-seeking behaviour (lacks euphoric activity).[4] The use of PCA with tramadol, a synthetic analogue of codeine that binds to mu opiate receptors and inhibits norepinephrine and serotonin uptake, for the control of pain associated with labour has been described.[5] A potent analgesic efficacy, equivalent to meperidine or morphine for moderate pain, along with negligible respiratory depressant activity and minimal side-effects makes it suitable for this technique.

Frank and co-workers compared the use of nalbuphine (3 mg) and pethidine (15 mg) PCA techniques in a double blind randomized trial on 60 patients during the first stage of labour.[6] Group mean values of pain scores of nalbuphine-medicated primiparous women were statistically lower than those of pethidine-medicated patients ($P<0.01$). No differences were noted in sedation, uterine contractions, maternal cardioventilatory variables, fetal heart rates or Apgar scores. Another group in a recent study report the use of patient-controlled meperidine (10–15 mg every 10 min) analgesia in 259 women of mixed parity in spontaneous labour at full term.[7]

Finally, Burrows and colleague studied 513 (7.6%) cases of thrombocytopenia occurring in 6715 consecutive deliveries. Of these cases, 65.1% consisted of healthy women in whom thrombocytopenia was incidentally discovered, 13.1% were healthy women with an obstetric or medical condition such as diabetes or premature labour and 21% were hypertensive patients and patients with immune thrombocytopenia.

This information, in association with that offered by the authors, helps us to understand better the way to deal with the labour analgesic requirements of the parturient with associated thrombocytopenia.

A. Anand
Department of Pain Management/Anesthesiology
Medical College of Wisconsin
Milwaukee
WI, USA

1 Thurlow JA, Waterhouse P. Patient-controlled analgesia in labour using remifentanil in two parturients with platelet abnormalities. *Br J Anaesth* 2000; **84**: 411–3
2 Beilin Y, Zahn J, Comerfold M. Safe epidural analgesia in thirty parturients with platelet counts between 69 000 and 98 000 mm^{-3}. *Anesth Analg* 1997; **85**: 385–8
3 Beilin Y, Bodian CA, Haddad EM, Leibowitz AB. Practice pattern of anesthesiologists regarding situations in obstetric anesthesia where clinical management is controversial. *Anesth Analg* 1996; **83**: 735–41
4 Vogelsang J, Hayes SR. Butorphanol tartrate (stadol): a review. *J Post Anesthsia Nurs* 1991; **6**: 129–35
5 Lewis KS, Han NH. Tramadol: a new centrally acting analgesic. *Am J Health-System Pharm* 1997; **54**: 643–5
6 Frank M, McAteer EJ, Cattermole R, Loughnan B, Stafford LB, Hitchcock AM. Nalbuphine for obstetric analgesia. A comparison of nalbuphine with pethidine for pain relief in labour when administered by patient-controlled analgesia (PCA). *Anaesthesia* 1987; **42**· 697–703
7 Sharma SK, Sidawi JE, Ramin SM, Lucas MJ, Leveno KJ, Cunningham FG. Cesarian delivery: a randomized trial of epidural versus patient-controlled meperidine analgesia during labor. *Anesthesiology* 1997; **87**: 487–94
8 Burrows RF, Kelton JG. Thrombocytopenia at delivery: a prospective survey of 6715 deliveries. *Am J Obstet Gynecol* 1990, **162**: 731–4

Editor—We thank Dr Anand for his interest in our case report.[1] We would like to reply to some of the points he raised. In our discussion, we stated that epidural analgesia for labour is not recommended if the platelet count is less than 100×10^3 ml^{-1} (normal $>150 \times 10^3$ ml^{-1}).[2] We accept that Beilin and colleagues reported no complications when the platelet count was less than 100×10^3 ml^{-1} in their series of 30 parturients.[3] Epidural haematoma, although infrequent, is a true emergency and must be decompressed within a few hours to prevent permanent neurological damage. Parturients who present with a low platelet count at time of delivery and in whom pregnancy is uneventful differ from those parturients with thrombocytopenia due to increased platelet destruction. An epidural for labour may be considered safe in a patient with a platelet count of less than 100×10^3 ml^{-1} if there is no risk that the platelet count has decreased further and that there is no associated platelet dysfunction or other coagulation abnormality.[2] We agree with Dr Anand that the whole clinical presentation should be taken into account when deciding on specific analgesic techniques.

Patient-controlled analgesia techniques are not new to obstetrics. We accept that various opioids have been used with a PCA device in labour,[4–7] but remifentanil may have advantages compared to other opioids due to its rapid onset time and rate of hydrolysis.

J. A. Thurlow
P. Waterhouse
Bristol, UK

1 Thurlow JA, Waterhouse P. Patient-controlled analgesia in labour using remifentanil in two parturients with platelet abnormalities. *Br J Anaesth* 2000; **84**: 411–3
2 Rolbin SH, Abott D, Musclow E, Papsin F, Lie LM, Freedman J. Epidural anesthesia in pregnant patients with low platelet counts *Obstet Gynecol* 1988; **71**: 918–20
3 Beilin Y, Zahn J, Comerfold M. Safe epidural analgesia in thirty parturients with platelet counts between 69 000 and 89 000 mm^{-3}. *Anesth Analg* 1997; **85**: 385–8
4 Vogelsang J, Hayes SR. Butorphanol tartrate (stadol): a review. *J Post Anesth Nurs* 1991; **6**: 129–35
5 Lewis KS, Han NH. Tramadol: a new centrally acting analgesic *Am Health-System Pharm* 1997; **54**: 643–5
6 Frank M, McAteer EJ, Cattermole R, Loughnan B, Stafford LB, Hitchcock AM. Nalbuphine for obstetric analgesia. A comparison of nalbuphine with pethidine for pain relief in labour when administered by patient-controlled analgesia (PCA). *Anaesthesia* 1987; **42**: 697–703
7 Sharma SK, Sidawi JE, Ramin SM, Lucas MJ, Leveno KJ, Cunningham FG. Cesarian delivery. a randomized trial of epidural versus patient-controlled meperidine analgesia during labor *Anesthesiology* 1997; **87**: 487–94

Difference in pre-intervention and post-intervention thromboelastography times

Editor—In the report by Gorton, Lyons and Manraj,[1] the difference in pre-intervention and post-intervention thromboelastography times is probably an artefact of sampling technique. The first sample was withdrawn through a 16-gauge cannula, whereas the second sample was taken through a 22-gauge cannula. There was thus a difference in the sampling technique. It is recognized that sampling blood through small bore needles can induce pre-activation of coagulation in the sample, resulting in artificially shortened clotting times. This could account for the difference in thromboelastography measurements found. To eliminate this error, the study should be repeated with both samples taken from the same place.

C. J. Richard
Department of Anaesthetics
Edinburgh Royal Infirmary
Edinburgh
UK

1 Gorton H, Lyons G, Manraj P. Preparation for regional anaesthesia induces changes in thromboelastography. *Br J Anaesth* 2000; **84**: 403–4

Editor—We are not aware of any evidence to suggest that coagulation as measured by thromboelastography (TEG) is influenced by the size of cannula used for venepuncture. To test this hypothesis, we performed TEG on five volunteers using a 16-gauge and a 22-gauge Venflon placed in opposite forearm veins, using a standardized technique with intradermal lidocaine. Blood taken from the larger cannula showed greater coagulability in all four TEG variables than that taken from the smaller cannula. For the difference to become statistically significant, we would have needed to study 150 to 200 subjects. We speculate that the larger cannula produces more endothelial damage, releasing coagulation activators.

It is likely that there is a cannula-induced artefact, although the differences are too small to be clinically significant. However, the changes seen are in the wrong direction to explain our original findings. The point we wished to make in our Short Communication was that TEG changes attributed to colloid infusions *in vivo* might have an alternative explanation. We hope that Dr Richard would approve if we acknowledge that a different cannula sequence would have supplied an unrelated explanation. We have sought to demonstrate that fine differences in technique can generate changes *in vivo* that might be erroneously attributed. We hope that in this respect, we share a common aim.

H. Gorton
Leeds
UK

Separating the treatment effect of atropine from its prophylactic benefits during inhalational induction of anaesthesia in young children

Editor—The interesting study by Shaw and colleagues[1] highlights the difficulties in separating the treatment effect of atropine from its prophylactic benefits during inhalational induction of anaesthesia in young children. Atropine does exactly what it says on the label, as shown by the reduction in excessive secretions and increased heart rate in those infants premedicated with 40 μg kg^{-1} orally. If the need to give succinylcholine during an inhalational induction is a proxy measure of airway difficulty, their finding that 15–16% of patients needed this intervention, regardless of whether they received atropine premedication, is interesting. Why give succinylcholine in this situation at all unless there is actual or impending airway difficulty? It is also noteworthy that similar proportions of patients experienced arterial desaturation below 94%. If these outcome measures are clinically relevant, then atropine premedication appears to offer no protection.

This study is a demonstration of the experienced anaesthetist's sixth sense, normally difficult to quantify but usefully summarized as the ability to anticipate and avoid trouble. It should not give comfort to the less experienced, however, because the authors have not shown that atropine premedication avoids the need to intervene with '...swift, appropriate airway management' to prevent clinically significant arterial desaturation.

Inhalational induction in infants remains a challenge even to the experienced anaesthetist and judicious premedication, whether sedative or anticholinergic, plays an important part. Just how the margin of safety can be increased, by which treatments and in which patients, needs further clarification.

P. Wolstencroft
M. A Stokes
Department of Anaesthesia
Birmingham Children's Hospital
Birmingham
UK

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[1] Shaw CA, Kelleher AA, Gill CP, Murdoch LJ, Stables RH, Black AE. Comparison of the incidence of complications at induction and emergence in infants receiving oral atropine vs no premedication. *Br J Anaesth* 2000; **84**: 174–8

Editor—Thank you for the opportunity to reply to Drs Wolstencroft and Stokes. We agree that the debate on appropriate premedication will continue but feel that our study has contributed to current knowledge. We have shown that the incidence of airway complications is significantly reduced in infants receiving 40 μg kg^{-1} oral atropine preoperatively. We have also shown that our patient population did not have an increased incidence of adverse effects attributable to atropine administration It is difficult to comment on succinylcholine administration as this was left to individual anaesthetic discretion. We agree that there was no statistically significant difference between the two groups for arterial desaturation below 94% but argue that reduction in airway complications may afford a greater 'margin of safety'. We feel that atropine premedication continues to have an important role in providing safe anaesthesia in infants.

C. Shaw
London
UK

Side-effects of alcoholic iodine solution (10%)

Editor—We read with interest the article by Raedler and colleagues[1] and subsequent correspondence regarding contamination of needles used during central neural blockade. Much of the correspondence related to the ideal solution for skin disinfection prior to needle placement. The ideal solutions suggested were chlorhexidine in alcohol or 10% iodine in alcohol.

We should like to report three cases of local inflammatory reactions following elective Caesarean section, which are thought to be related to the use of alcoholic iodine solution. Three healthy patients presented for elective Caesarean section, none gave any history of allergy to iodine. The operations were carried out under spinal anaesthesia by two different anaesthetists The usual skin preparation in our unit is aqueous iodine solution, but these patients were all prepared with alcoholic iodine solution (10%). All three patients subsequently developed superficial painful inflammatory reactions (including in one patient, blisters) on their buttocks where the iodine solution had run down their backs. To the best of our knowledge, the diathermy plates were correctly applied to their thighs. We have no explanation for the occurrence of these injuries other than a local concentration effect of pooled alcoholic iodine, perhaps exacerbated by heat and the occlusive effects of drapes and the rubber mattress of the operating table. Following these events, we discovered that similar problems had occurred in the unit some years earlier which had led to the introduction of aqueous iodine for skin preparation.

We would therefore urge caution in the widespread adoption of alcoholic iodine in skin preparation for regional techniques prior to Caesarean section. We recommend careful drying of patients' backs and buttocks before positioning on the operating table.

R. J. Chilvers
M. T. Weisz
Department of Anaesthesia
Peterborough Hospitals NHS Trust
Peterborough
UK

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[1] Raedler C, Lass Flörl C, Puhringer F, *et al.* Bacterial contamination of needles used for spinal and epidural anaesthesia. *Br J Anaesth* 1999; **83**: 657–8

Paediatric Intensive Care

Editor—Bennett's[1] review of Paediatric Intensive Care was interesting to read. The article provides an overview of the pathophysiology of meningococcal disease (MD) and its clinical manifestations. We would like to emphasize some aspects of the early management of this disease, which are likely to involve anaesthetist trainees. Trainees may not have encountered this patient group before and may not be familiar with publications on their management, as they are predominantly in paediatric journals.

At St Mary's Hospital, London, 425 critically ill children with MD were referred to the paediatric intensive care unit from 72 hospitals in the south east of England between June 1992 and September 1998. An algorithm has been developed for the early management of these patients from personal experience and practice.[2]

MD has a wide spectrum and may present either as meningitis, septicaemia or both. Early management of these cases is often carried out in district general hospitals, where anaesthetists are called upon for resuscitation, especially airway control, artificial ventilation and vascular access. Trainee anaesthetists faced with this challenging emergency need to be aware of the nature of the disease and the key resuscitation issues. Depending on whether septicaemia or meningitis predominates, the major clinical management problem will be either shock or raised intracranial pressure respectively; or in some cases both.

Few other diseases are as rapidly progressing as meningococcal septicaemia (MS), which has mortality of nearly 50%. Early recognition, aggressive resuscitation, specialist advice and transfer to a tertiary centre with paediatric intensive care have been shown to significantly reduce mortality in the paediatric population. There has not been such a decrease in mortality in the adult population.

Recognizing early features of compensated shock (tachycardia, cool peripheries, tachypnoea, confusion, poor urine output and increased capillary refill time) is the factor which determines outcome in this group of patients. Hypotension is a late and usually pre-morbid sign of shock in children. Treatment of shock involves careful attention to the ABC of resuscitation and early administration of oxygen. Intra-osseous access may be required in some infants with difficult peripheral cannulation. Fluid resuscitation with colloids, (we use 4.5% HAS), in 20 ml kg^{-1} boluses, should be promptly instituted in the face of early, compensated shock. Generalized capillary leak in MS may necessitate large amounts of fluid and if signs of shock persist, inotropic support may also be required. Dopamine and dobutamine infusions can be prepared as dilute solutions of 3 mg kg^{-1} in 50 ml crystalloid, and safely started via peripheral vascular access.

If signs of shock persist after 40 ml kg^{-1} fluid resuscitation, risk of pulmonary oedema is increased and we advocate early, elective intubation, using a rapid sequence induction (RSI) consisting of atropine, thiopental and succinylcholine. A cuffed endotracheal tube, where possible, facilitates the management of pulmonary oedema and is preferred Volume resuscitation and inotropic support, where indicated, should be continued before, during and after intubation. Boluses of colloid and inotropes must be drawn up for use if necessary during induction. Morphine or fentanyl and midazolam boluses may be used for adequate sedation and analgesia. In severe shock, epinephrine and norepinephrine may be required centrally. During volume resuscitation, regular review to assess adequacy of fluid replacement is mandatory and hourly urinary output monitoring serves as a sensitive marker for end-organ perfusion. A variety of metabolic, biochemical and haematological derangements may also occur which can contribute to myocardial depression and worsen shock. Hypoglycaemia, hypocalcaemia, hypokalaemia, metabolic acidosis, coagulopathy and anaemia must be anticipated, monitored (hourly) and corrected. If arterial pH is less than 7.2, bicarbonate should be infused.

Death in meningococcal meningitis (MM) is mainly due to raised intracranial pressure and children should be monitored for this complication. Coexistent shock, which may be seen in 40% of cases, must be treated as a priority. Management of raised intracranial pressure involves the principles of neurointensive care. Elevation of the head-end of the bed to 30° with the head midline; early, elective and controlled intubation following RSI, normocapnoea; minimal handling; and adequate sedation are the key principles. Seizures must be treated according to the APLS guidelines. An acute rise in intracranial pressure should be treated with mannitol 0.25 g kg^{-1} followed by frusemide 1 mg kg^{-1} and repeated if necessary. Internal jugular venous cannulation must be avoided. Lumbar puncture is strictly contraindicated in these patients.

Until the arrival of the retrieval team and transfer to a tertiary centre, anaesthetists play a significant role in influencing the early management and the outcome of these children. In our experience, a proportion of patients are suffering significant critical events secondary to inappropriate management. Protocols such as the one we outline provide uniform management guidelines for the multidisciplinary team caring for children with such complex and rapidly progressive disease, and aim to reduce regional variations in early morbidity.

A. Cooney
N. Mehta
Departments of Paediatrics and Anaesthesia
St Mary's Hospital
Paddington
London, UK

1 Bennett NR. Paediatric intensive care. *Br J Anaesth* 1999; **83** 139–56
2 Pollard AJ, Britto J, *et al* Emergency management of meningococcal disease. *Arch Dis Child* 1999; **90**: 290–6

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Book reviews

Nunn's Applied Respiratory Physiology, 5th Edn. A. B. Lumb. Published by Butterworth Heinemann, Oxford. Pp. 687; indexed; illustrated. Price £59.00 ISBN 0750631074

This text represents the fifth edition of this book. The previous editions were written and edited solely by Dr Nunn who has now handed the helm to Dr Lumb; the last of the research fellows in the Medical Research Council Division of Anaesthesia prior to Dr Nunn's retirement. Has the new broom swept clean or has a more traditional approach repackaged one of the best known and possibly most widely used text books emanating from British anaesthetic practice?

The aim of Dr Lumb, as outlined in the preface, was to provide the reader with the scientific background to allow a greater understanding of the problems of clinical practice. The book covers virtually every topic associated with the respiratory system in some degree. This means that anybody reading the book who is interested in looking further into a certain area will find some direction and guidance. As always, the book provides easy reading.

Previous editions of the book contained a number of short chapters giving basic information. These chapters were short and didactic, reflecting the fact that each was from a separate lecture given to students of medicine and anaesthesia. As might be anticipated, the illustrative diagrams used for these lectures were simply put together on a blackboard with chalk; reflected in the line diagrams of the text. This approach has not been modified by Dr Lumb. This is unfortunate as some of the diagrams are from publications 30 years ago and may have benefited from a more up to date explanation based on newer theories and concepts. In contrast, Dr Lumb has taken the opportunity to address certain of the criticisms of earlier editions to reorganize topics in various chapters so that the flow appears more logical. For example, previously separate chapters on pulmonary embolism and oedema have been amalgamated to be discussed in a chapter on pulmonary vascular disease.

The updating of each of the chapters and sections is patchy The chapter on aspects of ventilatory control and respiratory mechanics now includes an excellently illustrated section dealing with changes in position of the tongue during the induction of anaesthesia. There are also a number of illustrative examples of the separation of ventilation into rib cage and diaphragmatic components in various positions, with and without anaesthesia. This reflects the interest which Dr Lumb and his colleagues had at the time they were working with Dr Nunn. Despite this interest, this section also includes references to the effects of loading of breathing based on data from 40 years ago. Data which has been brought up to date by studies from other groups.

In contrast to the expanded sections dealing with airway mechanics, the sections dealing with inflammatory lung disease such as acute respiratory failure have been more superficially modified. On this topic it is unfortunate that Dr Lumb has fallen into the same trap as other authors and included a scheme to try to explain the inflammatory process based on novel molecular mechanisms. It is unfortunate that a more thorough review of the literature would show that very few, if any, of the mechanisms described has relevance to the pulmonary, as opposed to the systemic, circulation.

The description of molecular inflammatory mechanisms to the detriment of pathophysiology and therapy is also apparent in the section dealing with asthma. The half page allocated to principles of treatment of asthma follows a three page discourse on potential molecular mechanisms. This leads to more modern theories to explain airway collapse during expiration, such as wave speed theory and laminar and turbulent flows, not being fully explored There is also no discussion within the book of the potentially life saving use of less dense gas inhalation with helium in patients with obstructed airways.

The desire to modify the text, but not quite getting the full message home, is also illustrated in the section dealing with a variety of the more novel forms of pattern of ventilation, such as airway pressure release ventilation and pressure support/controlled ventilation. The physiological rationale for developing and performing these specific manoeuvres is limited. For example, the section discussing pressure controlled ventilation explains well the physical and mathematical mechanism(s) of effects on ventilation. However, in an earlier chapter, Dr Lumb suggests that this pattern of ventilation may fail to provide adequate alveolar ventilation. There is no explanation in the text for the pathophysiology of this lack of benefit and the reader is therefore left a little high and dry as to what might be a physiological basis for reduced alveolar ventilation using these patterns of mechanical ventilation.

Altogether, the author and publishers have provided a book which is well illustrated and laid out. I particularly liked the use of references at the end of each chapter rather than the total reference pooled at the end of the book. The criticisms outlined above are relatively minor and will surely be ironed out in future editions. In today's environment the book represents extremely good value for money. As with the four previous editions, I anticipate this version is destined for success and a place on the book shelf of departments of anaesthesia around the globe.

D. Royston

Conscious Sedation International Anesthesiology Clinics, Volume 37, Number 4, Fall 1999. L. Gilbertson (ed.). Published by Lippincott Williams and Wilkins, Philadelphia. Pp. 133; indexed; illustrated. Price £31.00.

The provision of adequate standards of safety, quality control and assurance during conscious sedation in clinics and departments away from traditional operating theatre environments, is one of the most challenging and controversial problems in current therapeutics. This volume outlines the various regulatory bodies and professional associations concerned with conscious sedation in the USA, notably the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and The American Academy of Pediatrics (APP). In the preface it is indicated that the JCAHO have identified a core responsibility for anesthesiologists in the implementation of conscious sedation by non-anesthetic providers. In the late 1980s it stated that the standards of care required for anaesthesia should also apply to sedation. More recently, in 1994, it required healthcare institutions to implement a single policy for Intravenous Conscious Sedation (IVCS) throughout their services and in 1997 this was expanded to include all sedatives and analgesics whatever the route of administration. This multiauthor volume outlines their experience and requirements in establishing a conscious sedation programme at the Brigham and Women's Hospital in Boston, Massachusetts in response to recommendations of the JCAHO. For example, Table 1, Chapter 1 summarizes hospital accreditation standards for anaesthesia to conscious sedation recommended by the JCAHO and the response of the Boston group to each requirement. It does not provide a prescriptive account of the administration of sedative

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drugs. However, the pharmacology sections describing the principle features of drugs used in conscious sedation are focused, succinct and relevant. There are excellent standard chapters on pre-operative assessment and patient selection, perioperative monitoring and management including complications. Of necessity, the sections on sedation in intensive care is constrained but nonetheless it includes the basic essentials of this subject. The final chapter on sedation in special situations is also brief but completes the settings in which IVCS is practised. This volume of the journal is concerned primarily with. the implementation of policies and training programmes; the maintenance of competency of physicians and nurse monitors; and improved strategies for the provision of quality control and assurance, together with audit. Although it is packed full of information it is well crafted and easy to read. One criticism is the use of the Ramsay sedation score, albeit in the intensive care setting (Hurford WE, pg 113), since it includes deep sedation which current opinion would regard as undesirable during general therapeutic interventions as it is indistinguishable from light anaesthesia.

Two of the more interesting chapters concerned with education and the role of non-medical personnel in this field were written by highly experienced nurses involved in the care of patients receiving anaesthetic, sedative and analgesic drugs. All those currently involved in revalidation in anaesthesia and sedation would benefit from perusal of this material, notably the section on competence versus competency validation (Robins, Elaine V, pg 64).

Finally, this is a major contribution to the literature in the increasingly important field of conscious sedation which, because of the large number of patients involved, could become increasingly litigious with high awards for brain damage and death. It provides guidelines for legislators, hospital and clinical managers and practitioners alike and should be available for anyone involved in this subject.

J. G. Whitwam

Anaesthesia for Obstetrics and Gynaecology. R. Russell (editor). Published by BMJ, London. Pp. 369; index; illustrated. Price £35 00. ISBN 0727912763

Anaesthesia for Obstetrics and Gynaecology is one of the titles in a series produced by the *BMJ* under the banner 'Fundamentals of Anaesthesia and Acute Medicine'. The series aims to review principal clinical topics, emphasizing recent developments and controversial issues, in order to prepare trainees for degrees and diplomas in anaesthesia It is not a comprehensive text but of the nine chapters one involves anaesthesia for gynaecological surgery by Kym Osborn and Scott Simmons. The editor, Robin Russell, has selected clinical anaesthetists from either the United Kingdom or Australia. The clinical science background for the book perhaps reflects this basis, for example, in the use of old nomenclature for opioid receptors and drugs (lidocaine). The format of the book is varied with bullet points, tables and flow diagrams interspersed with pages of text. The headings are clear although structural organization must at times have been difficult and occasional repetition of topics such as laparoscopy and thromboembolic prophylaxis has been inevitable

As an edited book specializing in anaesthesia for women, it is unfortunate that the front cover depicts a pregnant woman as a spinalized preparation, i.e. without a brain! Is this the image anaesthetists wish to present to others of their management of women? Women are known to differ from men, for example in pain responses, and the opportunity to explore these gender issues has been missed.

The twin chapters on pain relief in labour, one by Mark Scrutton on non-regional aspects, and the other by Michael Paech based on regional techniques, are comprehensive and adequate for trainees A wide range of clinical topics are introduced and well referenced. the mother with systemic infection, breastfeeding, instrumental delivery dates, consent, continuous spinal analgesia and paravertebral block, as well as the choice of epidural and combined spinal epidural

An expert in airway management, Richard Vanner, has written the chapter on general anaesthesia in obstetrics. A failed intubation drill is presented as a simple flow diagram and although not stressed, the risk of total spinal anaesthesia following epidural anaesthesia is briefly mentioned for women with a known difficult airway.

Pre-eclampsia is discussed both in the chapter on medical emergencies by Caroline Grange and in the patient with coexisting disease by Phillipa Groves and Michael Avidan. So-called medical emergencies include fetal distress and this section is well worth reading. It includes many useful tables and ideas, some of which are debatable, such as definition of urgency of Caesarean section, which is not referenced. Aspects of critical care are incorporated into the management of selected emergencies but without indexing. The concept of obesity as a coexisting disease with medical risks is pertinent. Although necessarily brief, the anaesthetic complications described in association with obesity relate to a significant proportion of the obstetric population.

Another welcome section is that of anaesthesia for non-obstetric surgery that is included in the chapter on maternal changes in pregnancy by James Eldridge. Information for women in this field of anaesthesia is not easily obtained and in this chapter the risk/benefit analysis is ably discussed The most common operation during pregnancy with fetal survival is cervical cerclage to repair an incompetent cervix Somehow it slips into this part of the text.

The chapter on the effects of anaesthesia and analgesia on the baby by Jackie Porter begins with methods of fetal assessment and covers all types of analgesic and adjuvant drugs used. There is a long section on drugs and breast-feeding, which is appropriate in the present climate of patient enquiry. Robin Russell continues this focus on postnatal care in a chapter on postnatal assessment. Basic outcome data should support audit and risk assessment and methods to do this are examined.

This is a book for an up to date review of analgesia and anaesthesia for obstetrics. In future, the basis for the wider remit of disorders of the reproductive system in women should be considered and the scientific basis developed for anaesthetists to relate to other professional groups working with women.

Anita Holdcroft

The Association of Anaesthetists of Great Britain and Ireland 1932–1992 and the Development of the Specialty of Anaesthesia Sixty Years of Progress in the Context of Scientific, Political and Social Change. Thomas B. Boulton. Published by Association of Anaesthetists of Great Britain and Ireland, London Pp. 785; indexed; illustrated. Price £30.00. ISBN 0953663906

The Association of Anaesthetists of Great Britain and Ireland was founded in 1932. This book tells its story over 65 years, to 1997. It is mainly the work of Dr T. B Boulton, a past President (1984–86) and former Editor of *Anaesthesia*, the Association's journal. 1993–1997 is described by a former Vice President, Dr Anna-Maria Rollin. Tom Boulton is well suited to his role through prolonged involvement with and obvious love for the subject. He set himself, and achieved, a gargantuan task, departing frequently from his main discourse to provide accounts of medical and medico-political progress contemporaneous with developments in anaesthesia, brief biographies and anecdotes about some of the more colourful or dramatic personalities, and personal commentary from time to time. (There is a hint amongst the acknowledgements that some of the personal commentary may have been attenuated by friends!) For future researchers there are five appendices and 2002 references.

It is those who have been closest to the Association, as officers, members of committees, or beneficiaries, who will find the greatest interest in the book. The emphasis is, at least in part, hegemonical. But I believe there is much of interest to the general (anaesthetist) reader, especially in the first six chapters. These tell of the evolution of anaesthetic practice in the Association's years before the National Health Service, and the major influence of the Second World War on the specialty. From uncertain beginnings, mainly at the hands of General Practitioners, an increasingly secure and clearly defined group of trained medical specialists emerges. The arrival of the NHS, in 1948, gave them enormous opportunities for improvement of skills and methods, developing sub-specialties of anaesthesia in obstetrics, neurosurgery and cardiac surgery – all of which combined to benefit the patient, not least by allowing surgical interventions which had not been possible hitherto. The contribution to all this by key figures acting for or with the Association is beautifully described. Even today, the events of these times set the specialty on a plane that is still the envy of the world.

At the outset, the purpose of the Association was to 'deal with the problems of the organisation of this branch of medicine'. Not unreasonably, this centred on professional status and remuneration. The Association does not deal directly with governments or hospital authorities in the matter of terms and conditions of service. That is the role of the British Medical Association (BMA). The Association, in common with similar specialist bodies in medicine, has developed and maintained a close relationship with the BMA. It is notable, however, that the BMA was not always conciliatory in response Some of the greater political achievements of the Association (in some aspects of salary and the demands in respect of the consultant grade in the new (1948) NHS) came from either bypassing the BMA or the patronage of more established bodies such as The Royal College of Surgeons of England. The development of the examination for the Diploma in Anaesthetics, in 1935, and convincing the General Medical Council of the need for better teaching for undergraduates are two important early credits for the Association.

Throughout its 65 years, the Association spent what some might regard as a disproportionate effort on the perceived inadequacies of dental anaesthetic fees, a problem that was never satisfactorily resolved for reasons that a student of elementary economics could have explained. Happily for the Association, they at least kept up with the best of the organizations that would claim to have addressed the safety of general anaesthesia for the dental chair, but patients still lose their lives.

The vexed question of the disparity between anaesthetic and surgical fees in the euphemistically-called independent sector of practice continues, although the rules of engagement and the arguments have changed.

In the modern setting, the Association has many facets to its activity which its founders would find strange, reflecting new dimensions in international exchange, audit (in which the Association was an early participant), special interest groups, education, guidelines, safety of practice, and counselling of sick doctors practising the specialty. Many of the considerations affecting modern anaesthetic practice extend across the remits of both the Association and The Royal College of Anaesthetists. The Association was, of course, the original petitioning body that caused The Royal College of Surgeons of England to set up the Faculty of Anaesthetists, in 1948, which in turn led to The Royal College of Anaesthetists of today. It is a matter of opinion, of course, but the strategies of some anaesthetists, in the 1970s and 1980s, purporting to reflect the feelings of the Association's Council of that time, caused enormous ill-feeling amongst leading and influential surgeons and at least some of the leaders of the specialty of anaesthesia. I am sorry this book does not make that clear. Had it done so, the mystery of the 'misgivings of some of the more conservative members (of the Faculty)' could cease to be a mystery: our profession was at risk of being split, possibly irrevocably. Happily, today, the College and the Association are collaborating amicably.

The entire specialty has cause to be grateful to Tom Boulton for collating such a wealth of material in a book which, against modern publishing standards, is a most handsome production.

Alastair A. Spence

Perioperative Medicine: Managing Surgical Patients with Medical Problems. A. Nicholls and I. Wilson (editors) Published by Oxford University Press, Oxford. Pp. 384; indexed. Price £19.95. ISBN 0-19-202975-1.

Occasionally a book comes along that you only wish you had possessed at an earlier point in your career. Medical house officers are well catered for with the *Oxford Handbook of Clinical Medicine*, but there has not, until now, been a comparable stalwart for the surgical house officer. This little book is tailor made for all such nervous house officers, as well as their slightly more confident senior house officers (especially those directly involved in the perioperative care of patients). With its small size and splash-proof cover, it is well designed to withstand the rigours of day-to-day ward life. It has a practical, down-to-earth approach, and should soon become an essential part of the junior doctor's paraphernalia.

There are a total of 26 contributors, most of whom are consultant anaesthetists working in Exeter. However, a significant number of the authors (including one of the editors) are from other specialties, which gives the book a truly multidisciplinary feel.

It is divided into three parts. The first, consisting of medical issues in perioperative care, deals with every day issues such as patient consent, postoperative nausea and vomiting, management of pain and the role of teamwork on the surgical ward. This advice tends to be precise and commits itself to actual figures and doses which, of course, is exactly what the junior doctor needs. I suspect that I was not the only house officer totally unsure about such problems as fluid requirements for postoperative patients, how many units of blood to crossmatch for a nephrectomy, or even how often morphine could be given. These are the sort of issues that junior doctors may feel awkward asking their busy senior colleagues about, but they are dealt with comprehensively in the book. However, it would be worth the trainee checking some of the details against local hospital policy.

The next section deals with the care of surgical patients with chronic medical disorders, from the obvious (ischaemic heart disease) to the more obscure (hereditary spherocytosis). Quite rightly, it avoids the temptation to over-discuss the interesting rarities and emphasizes the common problems (the chapter on cardiovascular disorders being the longest in the book). Again, the advice is practical and realistic.

The final section discusses medical emergencies in surgical patients Common problems are dealt with, such as the assessment and treatment of hypotension, breathlessness and postoperative oliguria. My main criticism of this section is that it may have been helpful to have made more use of algorithms and to have made the 'life or death' chapters more obvious to find. However, the section is very thorough and would certainly help the junior doctor to initiate treatment prior to the arrival of help. At the end of the book, there is a chapter on perioperative prescribing information, which includes the sensible advice to consult the British National Formulary if in doubt.

Overall, the individual chapters are short and easy to read, as well as being user-friendly for those who want to use them as a quick reference guide. Potential problem areas are clearly identified, with concise and to the point advice on how to resolve the problems. The large number of contributors results inevitably in a certain amount of duplication, although not as much as one might expect. For instance, antibiotic treatment for sepsis is dealt with in three separate parts of the book. There also seems to be a certain amount of unnecessary extra information in some of the chapters, which makes it difficult sometimes to locate the required facts.

I feel that, as a trainee nearing the end of my specialist registrar rotation, this is the sort of book I wish I had had in my pocket 10 years ago as a junior doctor (ironically, working at the same hospital as many of the authors). However, I also feel that I would have continued to use it as I approached my various FRCA examinations. It will be an easy book to surreptitiously slip into my bag once I am a consultant, to read a few pages between cases and use as a teaching aid for trainees. It is the sort of book that, given its convenient pocket size, could reverse the trend away from junior doctors not wearing white coats on the wards. This book needs to be kept by the bleep of every doctor involved in the every day level of caring for perioperative patients.

Jo Kerr

Guide to Contributors

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Dr J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005. E-mail: bja@liv.ac.uk

Papers

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publisher.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki and should normally include a statement of approval from an appropriate Ethics Committee. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted. Studies from the UK should specify the Home Office Licence number; from elsewhere, a statement of approval from an appropriate licensing authority.

Legal considerations

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the authors and publishers.

Preparation of manuscript

Four copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss. Where possible, manuscripts should also be submitted on disk. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the three other sets may be photocopies.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all the authors. There should be a clear declaration of any financial or commercial interest which any author may have in the material. The Editor may wish to see raw data if necessary.

Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary, including Keywords
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Illustrations

Title page

There should be a separate title page, including the name(s) and address(es) of all author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given and referenced at the appropriate place in the author list by superscript numbers. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spacing should be included.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, methods, results and conclusions, and normally should

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be of 50–150 words. It may be used as it stands by abstracting journals.

Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the international non-proprietary name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of results, while concise, should permit repetition of the investigation by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability.

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially. Individuals named must be given the opportunity to read the paper and approve their inclusion in the acknowledgements, before the paper is submitted.

References

There should be a list of references at the conclusion of the paper, commencing on a new sheet.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically.

References in text, tables and legend should be identified by arabic numbers appearing in the text in superscript, for example ^{5} or $^{5–7}$ or ^{5}<space>^{16} for unrelated references. When a table, figure is first mentioned, its reference must continue the sequence.

Use the style of references adopted by the US National Library of Medicine and used in *Index Medicus*. The titles of journals should be abbreviated.

The names and initials of more than six authors should be abbreviated to three authors followed by *et al.*

Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase 'in press' replacing volume and page number. Information from manuscripts submitted but not yet accepted should be cited in the test as unpublished observations.

Examples of correct forms of references:

Journals:

1. Brown BR jr, Gandolphi AJ Adverse effects of volatile anaesthetics *Br J Anaesth* 1987; **59**. 14–23

Chapter in a book:

2. Hull CJ. Opioid infusions for the management of postoperative pain. In Smith G, Covino BG, eds. *Acute Pain*. London. Butterworths, 1985; 155–79

Monographs:

3. Moore, DC. *Regional Block*, 4th Edn. Springfield, Illinois Charles C Thomas, 1979

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All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with Arabic numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used. Footnotes are not used.

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It should be noted that A4-size figures generated by computer are usually unacceptable (see Extended Guide to Contributors—*Br J Anaesth* 2000; **84**: 131–7).

General information

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Headings in the text. Three possible grades are available, and may be indicated by the following letters of identification.

A **Results (bold)**
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Symbols and abbreviations. In accordance with Editorial adoption of SI units, abbreviations and symbols should follow the conventions described in the booklet *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors* (D. N. Baron, ed.) (1988), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with 'z' rather than 's' spelling in, e.g. organize, organization.

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Authors are encouraged to submit short manuscripts suitable for rapid publication. In general, these should conform to the requirements outlined above, but with the following differences:

Format. Summary; Introduction (not headed); Methods and results; Comment.

Size. Not more than 6 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words).

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Each issue of the journal will contain correspondence. Correspondence arising from papers in a recent issue is published without delay, and for this reason, will be given priority over that pertaining to original research. The Editor may change, delete or modify in any way all items of correspondence.

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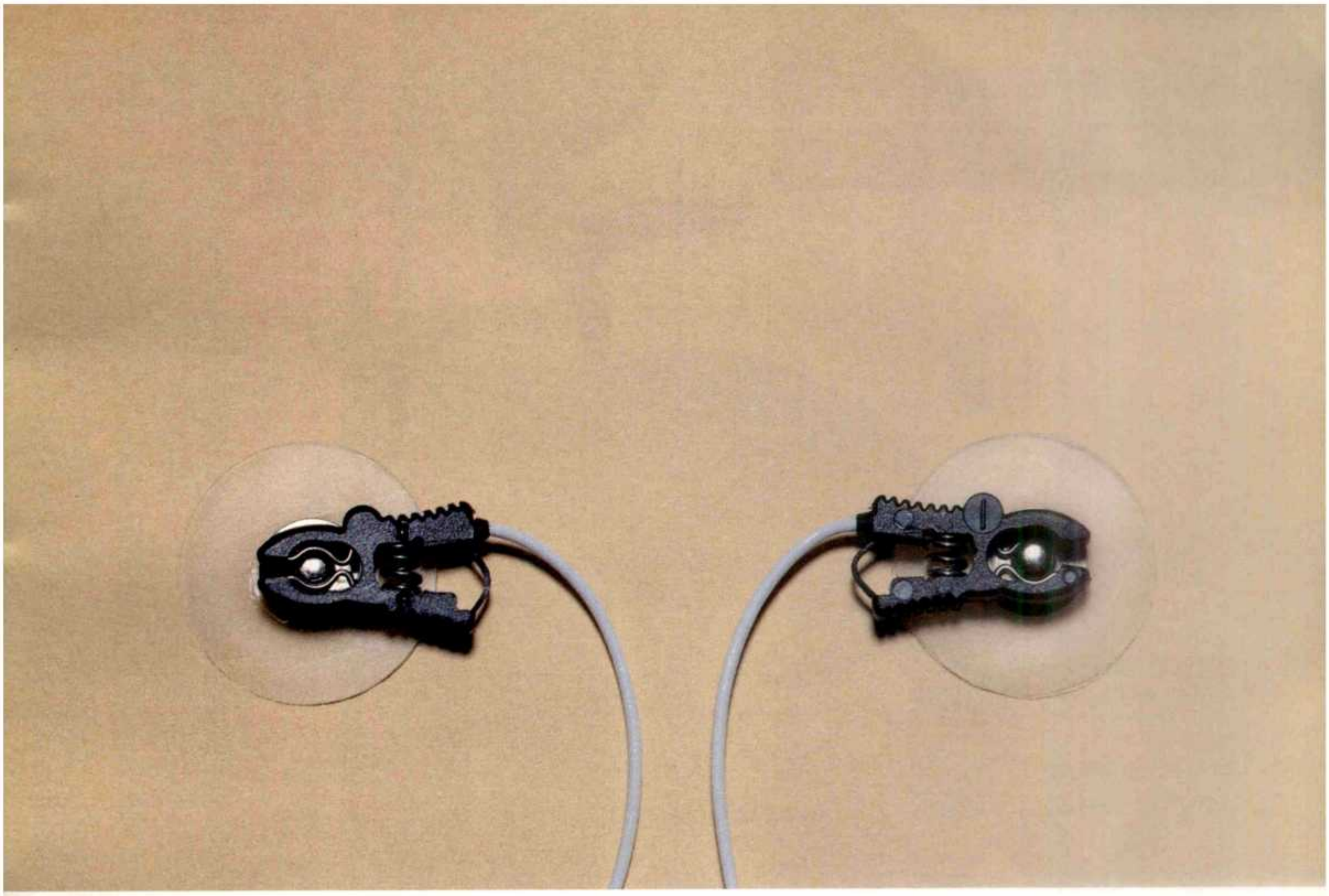

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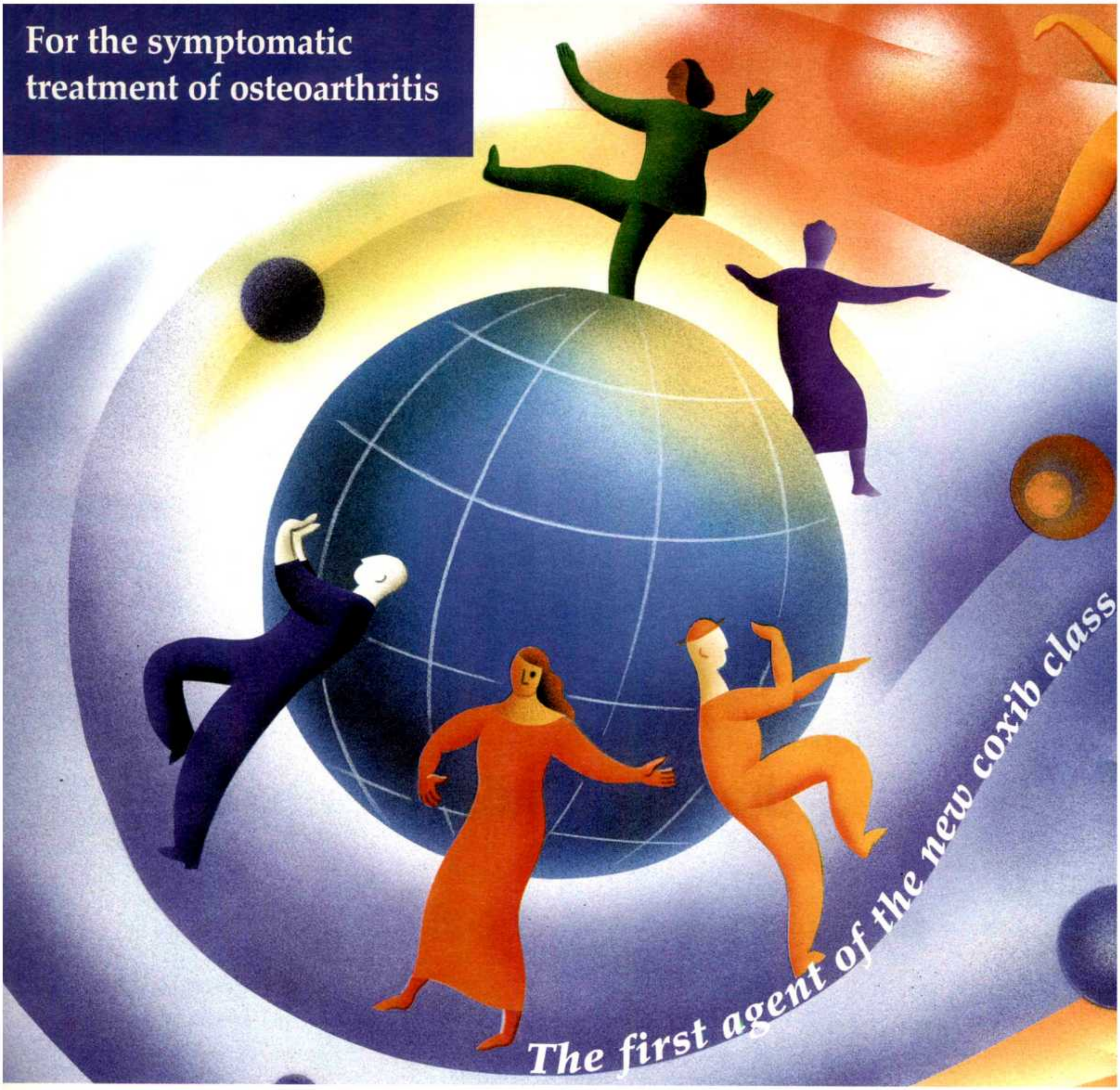
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The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded.

Elderly: Exercise care when increasing the dose from 12.5 mg to 25 mg.

Hepatic insufficiency: In mild hepatic insufficiency, do not exceed 12.5 mg once-daily.

Children: Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib.

Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension.

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

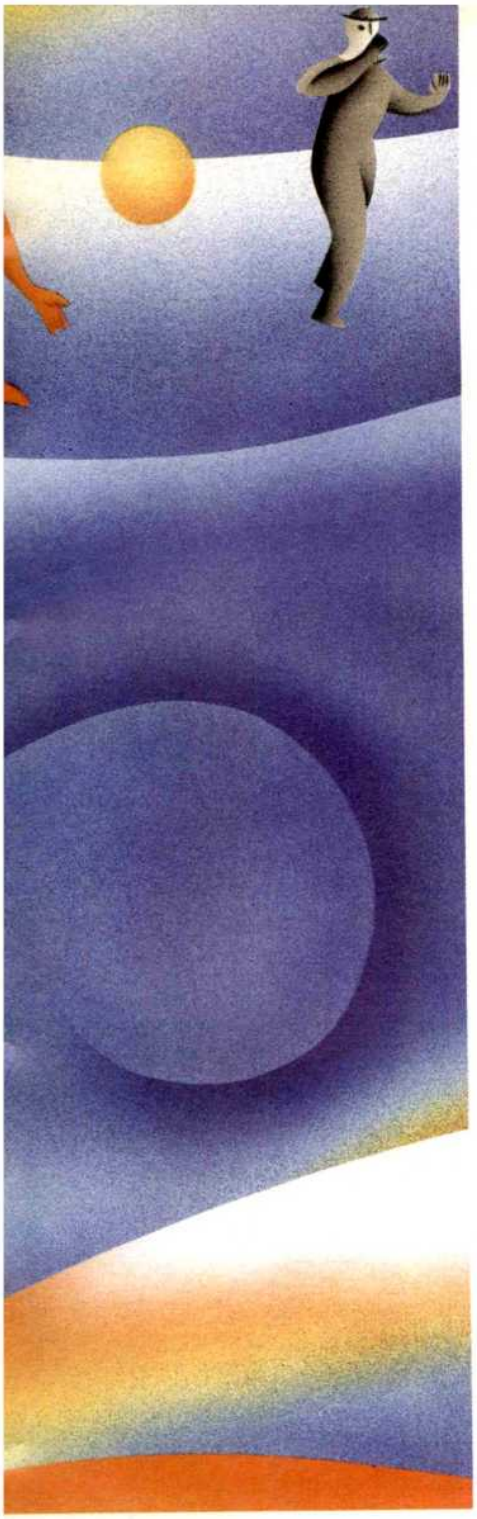
Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib. Rofecoxib may mask fever.

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone.This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of



In clinical studies: inhibits COX-2 but not COX-1[1]*

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* statistically significant inhibition of COX-1 has not been documented with any dose of VIOXX given to humans.

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rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with rofecoxib for one year or longer.

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

PACKAGE QUANTITIES AND BASIC NHS COST

Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58.

Oral Suspension 12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12.

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References:

1. Ehrich EW, Dallob A, De Lepeleire I et al. Characterization of rofecoxib as a cyclo-oxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999; 65(3):336-347.
2. Data on file, Merck Sharp & Dohme Limited.
3. Langman MJ, Jensen DM, Watson DJ et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;282(20):1929-1933.

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M.E.R.I.T. Centre Bradford Royal Infirmary, Bradford, UK – One day course in Spinal Endoscopy

Bradford, UK, 2000, September 15, 2000 and October 27, 2000

One day course with lectures, practical equipment demonstrations and observation of the technique in patients. Course material includes a comprehensive, practical guide to all aspects of the technique. Instrumentation is state-of-the-art, and it is anticipated that upon completion delegates will be in a position to consider setting up such a service in their own locality. On-going training will be offered.

Of interest to all those involved in the management and investigation of patients with back pain and sciatica as well as those involved with central neural blocks. Numbers of delegates strictly limited. Lunch will be provided.

For further information please contact:

Dr Jonathan Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford, BD9 6RJ.

Tel: +44 1274 364271/364253; Fax: +44 1274 366811; E-mail: merit.centre@mail.bradh-tr/northy.nhs.uk

Edinburgh Anaesthesia Festival

Edinburgh, August, 23–25, 2000

Organized by the Department of Anaesthetics, Royal Infirmary of Edinburgh, to coincide with the 2000 Edinburgh International Festival of the Arts. The 3-day programme consists of lectures and discussion on current topics in anaesthesia. The lecturers are from all parts of the United Kingdom and represent leading opinions in their field.

For further information: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW. Tel: +44 131 536 3652; Fax: +44 131 536 3672; E-mail: anaes@ed.ac.uk

The Fifth Annual Symposium of the Association for Low Flow Anaesthesia

Ulm/Neu-Ulm/Germany, September 8–9, 2000

For further information, please contact:

Priv. Doz. Dr Uwe Schirmer, Priv. Doz. Dr Thomas Marx, Department of Cardiac Anaesthesia, University of Ulm, Steinhövelstr. 9, D-89075 Ulm, Germany.

Tel: +49 731 5021521; Fax: +49 731 5026757; e-mail: alfa2000@gmx.net; congress homepage http://www.uni-ulm.de/alfa2000.

Annual Scientific Meeting in Anaesthesiology 2000

Hong Kong, September 8–10, 2000

We have great pleasure to advise you that the captioned Meeting will be held on 8–10 September 2000 at the Sheraton Hong Kong Hotel and Towers.

Provisional Scientific Programme. Airway Workshop (Prof. David Chung); Regional Anatomy, Workshop for Regional Blocks (Prof. Phillip Bridenbaugh); Evidence Based Medicine Workshop (Dr. Florence Yap and Dr. Gavin Joynt); Keynote Lectures: Perioperative Medicine – International Perspective (Chairman: Dr T. W. Lee) (Prof. Phillip Bridenbaugh); (Prof. Mathieu Gielen); (Dr Neil MacIntyre)

Panel Discussion: Medical Liability *vs* Litigation (Chairman: Dr T. W. Lee) (Mr Douglas Jones and Mr Chris Howse). Debates (Chairman: Dr C. T. Hung) (Prof. Michael Irwin and Prof. Warwick Ngan Kee *vs* Dr Phoebe Mainland and Dr Eddie Cheam); ICU Workshop Weaning from Ventilator (Dr Neil MacIntyre).

Keynote lectures: Perioperative Medicine—International Perspective Chairman: Dr T. W. Lee. The Road Ahead—Anaesthesiologist as Perioperative Physician (Prof. Phillip Bridenbaugh); Lung Protective Ventilatory Strategies (Dr Neil MacIntyre); Perioperative Pain Management—Comfort, Care and Cure (Prof. Mathieu Gielen).

Plenary session I. Test No Test? (Prof. Michael Irwin); Premedication—In or Out (Dr Jeffrey Kua); Perioperative Haemodynamic Goals (Dr Gavin Joynt).

Plenary session II. Preemptive Analgesia: Fact or Fallacy (Prof. Phillip Bridenbaugh); Anaesthetic Techniques—A Look into the Future (Prof Tony Gin); Continuous Spinal Anaesthesia—Is There a Role in Anaesthesia and Postoperative Analgesia (Prof. Mathieu Gielen).

Plenary session III. Chairman: Prof. Tom Buckley. Evaluation and Management of Postoperative Respiratory Insufficiency (Dr Neil MacIntyre); Acid-Base Secrets (Dr Ian Tan); Post-Anaesthetic Care—How Far Should We Go? (Dr C. T. Hung).

Refresher Course topics include: New Analgesic Agents (Dr S. L. Tsui); Anaesthesia for Cerebral Aneurysm Surgery (Dr Sathasivam Anandaciva); Advances in Clinical Measurement (Dr James Derrick); Paediatric Anaesthetic Emergencies (Prof. Cindy Aun); Day Case Anaesthesia (Dr Gwen Fok); Physiology of Consciousness (Prof. Michael Irwin); Spinal Anaesthesia for Day Surgery (Prof. Mathieu Gielen); Clinical Pharmacokinetics (Prof. Tony Gin); Anaesthesia for High-Risk Parturients (Prof. Warwick Ngan Kee); Physiology of Pregnancy (Dr K. K. Lam);

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Anaesthesia for Thoracic Aneurysms (Dr Das); and TEE (Dr Peter Hiong)

For further information please contact Ms Melissa Leung of the Federation of Medical Societies of Hong Kong. Tel: (852) 2527 8898; Fax: (852) 2866 7530

XIX Annual Congress of the European Society of Regional Anaesthesia Joint Annual Congress with EuroPain 8th European Conference on Pain Research

Rome, Italy, September 20–23, 2000

The congress will be held in the Sheraton Hotel.

Abstract deadline is June 1, 2000.

For further information, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 5643; Fax: +032 2 346 5435;
E-mail: dionne@options.com.cy

Collaborative Conference between Bournemouth University and Salisbury Health Care NHS Trust

Salisbury, UK, September 21, 2000

Day Surgery Conference at Salisbury District Hospital.

For further information please contact: Sam Williams, Administrative Assistant, IHCS, Bournemouth University, Royal London House, Christchurch Road, Bournemouth, BH1 3LT. Tel: +44 (0)1202 504196

Refresher Course in Anaesthesiology

Durban, South Africa, September 22–23, 2000

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Surfactant 2000

From Trier to Basle September 23–29, 2000

This is an international floating congress on the rivers Mosel and Rhine. All aspects of surfactant (basic science/clinical applications) will be addressed.

For further information, please contact:

Dr B. Lachmann, Department of Anesthesiology, Erasmus University Rotterdam, Postbox 1738, 3000 DR Rotterdam, The Netherlands.
Web site: http://www.floating-congress.vet.uu.nl

13th Annual Congress of the European Society of Intensive Care Medicine

Rome, Italy, October 1–4, 2000

For further information, please contact:

ESICM Congress Secretariat, 40 Avenue Joseph Wybran, B-1070 Brussels, Belgium.

Tel: + 32 2 559 0355; Fax: +32 2 527 0062; E-mail: public@esicm.org; Internet http://www.esicm.org

Dingle 2000 – Current Controversies in Anaesthesia and Perioperative Medicine

Dingle, County Kerry, Ireland, October 4–8, 2000

University College London Hospitals Centre for Anaesthesia announce a call for abstracts: there is an opportunity to submit work for poster presentation and selected finalists will be invited to give an oral presentation (prizes totalling £1000). Any research is acceptable provided it has not been published in any peer reviewed journal by the abstract deadline of 30 June 2000.

For further abstract and meeting registration details please contact:

Dr Monty Mythen, Centre for Anaesthesia, Room 103, 1st Floor Crosspiece, Middlesex Hospital, Mortimer Street, London, W1N 8AA, UK.

Tel: +44 20 7380 9477; Fax: +44 20 7580 6423,
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Part I (MCQ), October 7, 2000

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Wood Library-Museum's Quadrennial Laureate of the History of Anesthesia Prize

Members of the Editorial team of the *BJA* are pleased to announce that, Dr Thomas B. Boulton (UK) and Dr Norman A. Bergman (USA) are to be awarded the Wood Library –

Museum's quadrennial Laureate of the History of Anesthesia Prize at the annual meeting of the American Society of Anesthesiologists in October 2000, in San Francisco.

We offer our hearty congratulations to Dr Boulton, and to the family of Dr Bergman, who unfortunately died recently.

Awareness during Anesthesia—The 2000 *Anesthesiology* Journal-sponsored Symposium at the ASA Meeting

San Francisco, California, October 17, 2000, 9:00–12:30

The moderators will be Alex S. Evers MD (Washington University, St Louis) and Richard B. Weiskopf MD (University of California, San Francisco)

Awareness during anaesthesia is a potential problem of concern to clinicians and the public. There are clear cases of patients having been unintentionally awake during anesthesia and surgery and other cases for which 'awareness' was not as clearly delineated. 'Awareness' during anaesthesia and surgery can result in 'post-traumatic stress syndrome'.

This symposium will include invited speakers and a discussion session, as well as an opportunity to view selected abstracts. Abstracts in the following areas are considered appropriate for submission:

(i) epidemiology of 'awareness' during anaesthesia,
(ii) monitoring of depth of anaesthesia,
(iii) prevention of awareness during anaesthesia,
(iv) treatment of syndromes resulting from awareness during anaesthesia.

Abstracts should be submitted via the regular Annual Meeting procedures by April 1, 2000. *Online submission is available.* Abstracts requesting consideration for presentation at this symposium will undergo an additional review in addition to the standard ASA abstract review process. If you would specifically like your abstract considered for inclusion in the symposium, please check the special box that can be found on the cover letter/form which must accompany your submission. If you need abstract submission materials, please contact the American Society of Anesthesiologists:

American Society of Anesthesiologists, 520 N. Northwest Highway, Park Ridge, IL 60068–2573, USA.

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Haemostasis and Transfusion—Perioperative Management in Elderly Patients

Graz, Austria, October 27 and 28, 2000

This symposium has been organized by the Department of Anaesthesiology and Intensive Care Medicine, University of Graz and Department of Anaesthesiology, University of Munich.

The preliminary programme includes: haemostasis and transfusion, and perioperative management in elderly patients.

For further information contact: M. Neuray/G. Taucher, Department of Anaesthesiology and Intensive Care Medicine, LKH-Universitätskinikum Graz, Auenbruggerplatz 29, A-8036 Graz, Austria. Tel: +43 316 385 3027; Fax: +43 316 385 4664; E-mail: haemostasis@kfunigraz.ac.at. www.kfunigraz.ac.at/uanwww/haemostasis.htm

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Singapore November 29–December 3, 2000

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For further information, please contact:

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5th International Conference on Memory, Awareness and Consciousness – Pharmacology and Impact on Surgical and Critically Ill Patients

New York City, USA, June 1–3, 2001

This conference builds on the tradition of the previous Memory and Awareness in Anesthesia Conferences, and will focus on the following topics: measurement and monitoring of memory function, awareness and consciousness;

interaction of anesthetic and sedative drugs with the mechanisms of consciousness, awareness and memory processes; consequences and treatment of unwanted awareness or memory function during surgery or critical care; impact of surgery, anesthesia and critical care on cognitive and psychological processes; neuroimaging and mapping of consciousness, memory, awareness and pharmacologic effects on them in the CNS.

Deadline for abstracts: December 10, 2000.

For further information contact us via e-mail at mac@mskcc.org or visit our web site www.maacc.org or by mail: Ruth Reinsel, PhD, Dept of Anesthesiology/CCM, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10021, USA.

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For information and abstract forms contact: Helen Phillips, Box 1010, Mt. Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029-6574, USA.

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For further information on the congress, please contact:

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ESA 8th Annual Congress

(European Society of Anaesthesiologists)
Gothenburg, Sweden, April 10, 2001

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16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

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German Congress of Anaesthesiology 2001 (DAK 2001)

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For further information please contact:

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Editorial I

Metabolic support of critically ill patients: parenteral nutrition to immunonutrition

The adaptive metabolic changes that occur during starvation were described in detail over 30 years ago and are an excellent example of an integrated physiological response that conserves body protein and maintains normoglycaemia.[1] Critically ill patients are often malnourished and then starved for several days whilst undergoing the hormonal, metabolic and inflammatory changes that are commonly referred to as the 'stress response'.[2] It seems intuitively obvious, therefore, that feeding these patients during the gross catabolic phase of their illness should be beneficial. For many years, the best route for nutritional support was not clear and it is only in the past decade that there has been general agreement that enteral feeding is the method of choice.[3] However, some patients do not tolerate enteral feeding or do not obtain sufficient intake orally or enterally to meet their nutritional needs. Total parenteral nutrition (TPN) may be used in these patients either as a supplementary feed or as the only source of nutrition. Evidence to support the beneficial effects of TPN in critically ill patients has been lacking despite studies going back to the 1970s. A meta-analysis of studies of parenteral nutrition up to 1986 found only 11 trials that were randomized or quasi-randomized, and concluded that perioperative TPN was not justified in unselected major surgery.[4] A further meta-analysis of TPN was published in 1998 by Heyland and colleagues with the objective of examining the relationship between TPN and mortality and complication rates in the critically ill.[5]

The authors initially identified 153 citations from a bibliographic search for the years 1980–1998, and a further 57 articles were found from a review of reference lists and personal files. They examined only studies that evaluated the use of supplementary TPN in patients already receiving enteral feeds or studies of TPN in patients who were otherwise receiving standard care of oral food and i.v. glucose. Studies comparing TPN with enteral feeding or other forms of TPN were excluded. Only 26 randomized trials involving 2211 patients were suitable for evaluating TPN under these conditions.

The primary outcome was perioperative mortality and the secondary outcome was the rate of major complications. The investigators carefully defined major complications and differentiated them from minor complications, such as wound infection, atelectasis, urinary tract infection and phlebitis. Data on the duration of hospital stay were not aggregated into the analysis because of the variable and infrequent reporting methods. We have previously drawn attention to the problems inherent in attempting to use length of hospital stay as a measure of outcome.[6] To try to explain the heterogeneity of the data, the authors developed several hypotheses before undertaking the statistical analysis. They looked at the nutritional status of the patients, the methodological quality of the study, the date of publication and the use of lipids, and compared surgical with critically ill patients.

The results, aggregated from 26 studies, showed no effect of TPN on the mortality:risk ratio, which was 1.03 (95% confidence interval 0.81–1.31). There was a slight decrease, which was not statistically significant, in major complications in patients receiving TPN in the 22 studies in which these were recorded (risk ratio 0.84, 95% confidence interval 0.64–1.09). When the *a priori* hypotheses were examined to try to explain these results, it was found that a significant beneficial effect of TPN on major complications was present in malnourished compared with nourished patients, in studies with a low methodological quality score, in studies published earlier than 1988, and in surgical rather than critically ill patients. The only hypothesis that did not show a significant interaction with the complication rate was the use of lipids. It is notable that there was an increased incidence of major complications in critically ill patients receiving TPN that nearly achieved statistical significance (risk ratio 2.40, 95% confidence interval 0.88–6.58). In contrast, when these hypotheses were examined using mortality as the end-point, only one remained statistically significant in favour of TPN: the surgical patient compared with the critically ill patient (P=0.03). Furthermore, the mortality rate of critically ill patients receiving TPN was significantly increased (risk ratio 1.78, 95% confidence interval 1.11–2.85). Only 14 studies reported the effects of TPN on the duration of hospital stay, and in eight studies it was shorter in the control group.

Heyland and colleagues comment that, in spite of their intention to summarize the evidence of the effect of TPN on

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critically ill patients, the meta-analysis of 26 studies included only six studies of typical intensive care unit (ICU) patients. In particular, there were no studies of medical ICU patients or of patients with sepsis, and only limited assessment of trauma patients. It is common practice to aggregate studies of major surgical and ICU patients on the assumption that the physiological responses to injury and starvation are similar. But the subgroup analysis indicates that, with TPN, the complication rate and mortality rate were significantly greater in critically ill patients than surgical patients. It is no longer appropriate to apply data derived from studies of major surgery to ICU patients.

The results of the meta-analysis do not support the continuing use of TPN in critically ill patients. Indeed, the authors suggest that the only possible use for TPN may be in patients who cannot tolerate enteral nutrition. Since this view was based on a single study of surgical patients, in which TPN was no better than i.v. glucose, its relevance to critically ill patients must be doubtful.[7] Proponents of the continuing use of TPN in the ICU must provide evidence of benefit in the face of the unambiguous conclusions of the recent meta-analysis. In our view, TPN in the critically ill patient is of historical interest only, and this form of nutritional support should be confined to the malnourished, surgical patient.

With the popularization of the enteral route for feeding has come the realization that the incorporation of other compounds in the standard enteral feed may have beneficial effects on the metabolic, inflammatory and even immune response to injury. Novel substrates, such as medium-chain and short-chain fatty acids, glutamine and branched-chain amino acids, have been investigated.[8] More recently, attention has turned to the use of arginine, glutamine, nucleotides and omega-3 fatty acids as immunomodulators. The notion is simple and attractive: enhance immune function in the critically ill by the use of key nutrients in the enteral feed and the incidence of infectious complications and even the mortality rate should be improved. Immunonutrition was reviewed last in this journal in 1996.[9]

The most commonly used commercial preparation, Impact, contains the basic amino acid arginine, omega-3 fatty acids and RNA. The evidence to support the immune-enhancing properties of these three compounds is of varying quality. There is a considerable literature on the immunological effects of arginine and also of glutamine, which is incorporated in another commercial preparation, Immun-Aid. These amino acids enhance cellular immunity, modulate tumour cell metabolism, augment lymphocyte and macrophage proliferation (particularly glutamine), improve wound healing and decrease nitrogen loss post-operatively.[10–13] The ability of glutamine to maintain intestinal barrier function and prevent the translocation of bacteria and endotoxins from the gut lumen to the circulation may be particularly important in critically ill patients.[14] There are other properties of arginine that may also be important in modifying the physiological responses to injury. Arginine stimulates the secretion of several hormones, including the anabolic hormone insulin, and prolactin and growth hormone.[15] It may also be involved in the local regulation of tissue blood flow as it is a precursor of nitric oxide.[16]

The omega-3 fatty acids were thought initially to enhance immune defences through increased production of prostaglandin E_3 (PGE_3), which is less immunosuppressive than PGE_2, which is usually released in the inflammatory response. PGE_3 down-regulates the production of the proinflammatory cytokines tumour necrosis factor-α and interleukin-Iβ (IL-Iβ), and the major cytokine IL-6. The omega-3 fatty acids also have effects on the release of thromboxane A_2 and PGI_2 (prostacyclin), and inhibit a variety of cellular and humoral immunological mechanisms. The effects of these compounds on immune function have been reviewed in detail, but the literature pertains mainly to surgical oncology patients.[17 18]

The administration of RNA or synthetic polynucleotides to enhance immune function is less convincing. Dietary nucleotides are essential for cell-mediated immunity and T-lymphocyte function.[19 20] However, most experimental work has been undertaken in animals using nucleotide-free diets over several weeks, and the relevance of much of these data to critically ill patients is obscure. In 1995, Heyland and colleagues reviewed the available studies and concluded that there was little evidence to support the use of dietary RNA supplementation in patients.[21] We suggest that this opinion is still valid.

Cerra and colleagues published a preliminary study in 1990 that showed the effects of a combination of nutrients in enhancing immune function in ICU patients.[22] This seminal work has stimulated further clinical studies in the past decade to examine not only immune function but also the potential clinical benefits in patients receiving immunonutrition. In 1999, Heys and colleagues reported a meta-analysis of randomized controlled trials of enteral immunonutrition in patients with critical illness and cancer.[23] The authors conducted a search for articles published between 1990 and 1998 and identified 11 randomized controlled trials evaluating the use of enteral nutritional support supplemented with combinations of key nutrients (immunonutrition) versus standard enteral nutrition. They evaluated only the clinical outcome: major infectious complications, nosocomial pneumonia alone (as a possible indicator of changes in immune function) and mortality. The duration of stay in the ICU and hospital were analysed when the information was documented. In eight studies, Impact (L-arginine, *n*-3 essential fatty acids and RNA) was used, Immun-Aid (L-arginine, L-glutamine, branched-chain amino acids, *n*-3 essential fatty acids and RNA) was used in two studies, and in one study the experimental diet was enriched with L-arginine and L-glutamine.

When the data were aggregated for the meta-analysis, there was a significant decrease in the risk of developing major infectious complications in the immunonutrition group (odds ratio 0.47, 95% confidence interval 0.32–0.70). However, there was no significant improvement in the incidence of nosocomial pneumonia (odds ratio 0.91, 95% confidence interval 0.53–1.56). Supplemented enteral nutrition was associated with a significant decrease in the duration of hospital stay of 2.5 days (95% confidence interval 1.0–4.0), although the duration of stay in the ICU did not change in the four studies in which this variable was noted.

At first sight, the results of the meta-analysis are impressive, with a lower risk of developing a major infectious complication and a shorter duration of hospital stay in the patients given immunonutrition. In contrast, however, there was an increased risk of death in the immunonutrition group (odds ratio 1.77, 95% confidence interval 1.00–3.12) that just failed to reach statistical significance. It is possible that the lower incidence of major infections and shorter hospital stay in the supplemented group may simply have been a consequence of the increased early mortality. There is no mention in most of the studies analysed of the bias of death on these variables and the need to 'censor' this effect. Indeed, there is an uncanny parallel between the findings of the meta-analysis and a study of immunonutrition in critically ill patients that was published in 1998 after the literature search.[24] In this recent investigation of 101 patients, the use of Impact was found to have no effect on mortality (48% in the Impact group, 44% in the control group), but was associated with a significant reduction in the need for pulmonary ventilation (6.0 *vs* 10.5 days, $P = 0.007$) and a decrease in the duration of hospital stay (15.5 *vs* 20 days, $P = 0.03$). When the duration of hospital stay of patients who died was removed from the results, the difference was no longer statistically significant (P=0.08).

It is important to note that, in the meta-analysis of immunonutrition, the majority of studies (six out of 11) examined surgical patients usually with an upper gastrointestinal malignancy. In four of the surgical studies no patients died. Only five studies investigated critically ill patients, and these were predominantly patients with major trauma. As in the TPN meta-analysis,[5] results from typical ICU patients were not available to assess the effects of immunonutrition.

Obviously, there is a need for further randomized controlled studies of immunonutrition in critically ill patients. Future studies must have adequate statistical power, well-described patient groups, precisely defined nutritional regimens, an appropriate control nutritional group and accurate outcome measures. The results of the meta-analysis of immunonutrition hint at beneficial effects: decreases in the incidence of major infectious complications and in the length of hospital stay. It is imperative that appropriate studies of immunonutrition are undertaken to avoid the confusion and uncertainty that has accrued after 25 years of research into TPN. At present, the value of immunonutrition in critically ill patients is not proven.

B. C. Kennedy
G. M. Hall
St George's Hospital Medical School
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References

1 Cahill GF, Herrera MG, Morgan AP, et *al*. Hormone–fuel interrelationships during fasting. *J Clin Invest* 1996; **45**: 1751–69

2 Rolih CA, Ober KP. The endocrine response to critical illness. *Med Clin North Am* 1995; **79**: 211–4

3 Heyland DK, Cook DJ, Guyatt GH. Enteral nutrition. a critical appraisal of the evidence. *Intensive Care Med* 1993, **19**: 435–42

4 Detsky AS, Baker JP, O'Rourke K, Goel V Perioperative parenteral nutrition: a meta-analysis. *Ann Intern Med* 1987, **107**: 195–203

5 Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. *JAMA* 1998; **280**: 2013–19

6 Chumbley GM, Hall GM. Recovery after major surgery: does the anaesthetic make any difference? *Br J Anaesth* 1997; **78**, 347–9

7 Sandstrom R, Drott C, Hyltander A, et *al* The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. *Ann Surg* 1993; **217**: 185–95

8 Grant JP. Nutritional support in critically ill patients. *Ann Surg* 1994; **220**: 610–6

9 O'Leary MJ, Coakley JH. Nutrition and immunonutrition. *Br J Anaesth* 1996; **77**: 118–27

10 O'Riordain MG, Fearon KCH, Ross JA, et *al*. Glutamine-supplemented total parenteral nutrition enhances T-lymphocyte response in surgical patients undergoing colorectal resection. *Ann Surg* 1994; **220**: 212–21

11 Park KGM, Heys SD, Blessing K, Eremin O, Garlick PJ Stimulation of human breast cancers in vivo by dietary L-arginine. *Clin Sci* 1992; **82**: 413–7

12 Ardarwi MSM. Glutamine and glucose metabolism in human peripheral lymphocytes *Metabolism* 1988; **37**: 99–103

13 Stehle P, Mertes N, Puchstein C, Zander J, Albers S, Lawin P. Effect of parenteral glutamine peptide supplements on muscle glutamine loss and nitrogen balance after surgery. *Lancet* 1989, **I**: 231–3

14 Windmueller HG, Spaeth AE. Uptake and metabolism of plasma glutamine by the small intestine. *J Biol Chem* 1974; **249**: 5070–9

15 Chang DW, DeSanti L, Demling RH. Anticatabolic and anabolic strategies in critical illness: a review of current treatment modalities. *Shock* 1998; **10**: 150–60

16 Gianotti L, Alexander JW, Pyles T, Fukushima R. Arginine-supplemented diets improve survival in gut-derived sepsis and peritonitis by modulating bacterial clearance. The role of nitric oxide. *Ann Surg* 1993; **217**: 644–53

17 Heys SD, Park KGM, Garlick PJ, Eremin O. Nutrition and malignancy: implications for surgical practice. *Br J Surg* 1992; **79**: 614–23

18 Heys SD, Gough DB, Khan L, Eremin O. Nutritional pharmacology and malignant disease: a therapeutic modality in patients with cancer? *Br J Surg* 1996; **83**: 608–19

19 Van Buren CT, Kulkarni AD, Schandle VB, Rudolph FB. The

influence of dietary nucleotides on cell-mediated immunity. *Transplantation* 1983; **40**: 694–7

20 Rudolf FB, Kulkarni AD, Fanslow WC, Pizzini RP, Kumar S, Van Buren CT. Role of RNA as a dietary source of pyrimidines and purines in immune function. *Nutrition* 1990; **6**: 45–52

21 Heyland DK, Cook DJ, Guyatt GH. Does the formulation of enteral feeding products influence the infectious morbidity and mortality rates in the critically ill patient? A critical review of the evidence. *Crit Care Med* 1995; **22**: 1192–202

22 Cerra FB, Lehman S, Konstantinides N, Konstantinides F, Shronts EP, Holman R. Effect of enteral nutrient on in vitro tests of immune function in ICU patients: a preliminary report. *Nutrition* 1990; **6**: 84–7

23 Heys SD, Walker LG, Smith I, Eremin O. Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. *Ann Surg* 1999; **229**: 467–77

24 Atkinson S, Sieffert E, Bihari D. A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill. Guy's Hospital Intensive Care Group. *Crit Care Med* 1998; **26**: 1164–72

Editorial II

Safe placement of central venous catheters: where should the tip of the catheter lie?

Central venous catheters are ubiquitous in modern hospital and ambulatory medicine, with up to 6 million insertions per year in the USA[1] and 200 000 per year in the UK.[2] Despite this, there is still considerable doubt as to what constitutes optimal practice in terms of catheter composition, route of placement and the minimization of complications such as catheter-related sepsis, thrombosis and vessel perforation. In this issue of the journal, Schuster and colleagues describe an elegant post-mortem, radiological study of pericardial anatomy.[3] This work is based on the premise that, in order to prevent atrial or ventricular perforation and subsequent cardiac tamponade, the central venous catheter tip should not lie within the boundaries of the pericardial sac. In seeking to prevent this dramatic but rare complication are we exposing the patient to other equally serious but more insidious complications? The answer is probably yes. These issues are explored in this editorial.

Catheters will generally function equally well for pressure measurement and fluid infusion if the tip is situated in any major vein, above or below the heart. For dialysis or the infusion of irritant/hypertonic fluids, a high rate of blood flow past the catheter tip is desirable and this requires the placement of the luminal opening in as large a vessel as possible. However, the package inserts of many central venous catheters give very strong warnings about the absolute requirement for catheter tips to lie outside the heart to avoid perforation and subsequent pericardial tamponade.[4] In the USA, the Food and Drug Administration has issued advice emphasizing this point. This advice is based on numerous case series reporting the association between intracardiac placement of the catheter tip and (usually fatal) tamponade.[1 5–7] Authors of recent case series have acted as expert witnesses in cases of litigation related to fatal tamponade.[1 5] These experts may have been chosen for their polarized opinions. The outcome of such litigation has dictated the response of regulatory authorities and manufacturers. Despite this, the level of awareness of the issue amongst physicians, anaesthetists and radiologists was reported in 1995 to be low.[5]

Cardiac tamponade related to central venous catheterization follows a predictable pattern. Most cases occur in the first week after insertion.[5 6] Chest pain, nausea, dyspnoea, cyanosis, tachycardia, hypotension, engorged neck veins and pulsus paradoxus may occur hours before decompensation. The correct clinical diagnosis is rarely made and cardiac arrest usually ensues, with a mortality exceeding 70%. In most cases, review of the chest radiograph taken before tamponade reveals the catheter to be inside the cardiac silhouette.[5] At post-mortem, the fluid removed from the pericardium may be serous or serosanguinous, or may resemble the fluid being infused before tamponade. Interestingly, in a small proportion of patients it is not possible to find a definite track through the myocardium.

The incidence of tamponade is impossible to know precisely. Since the introduction of central venous catheterization in the 1950s, hundreds of millions of catheters have been inserted. Over the same period, the number of reported cases of associated tamponade is in the hundreds. Thus, even allowing for unrecognized and unreported cases, the scale of the problem is put into perspective. Experience with transvenous cardiac pacing is also instructive: the deliberate placement of transvenous pacing wires into the right atrial or ventricular wall very rarely results in tamponade.[8] To prevent tamponade, it would appear reasonable to avoid placement of the catheter tip within the right ventricle or deep into the right atrium (RA). However, there is increasing

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recognition that placing the tip in positions above the RA is also associated with significant complications.

Perforation

Catheter perforation of the central veins has been widely reported and may result in pleural effusion, hydrothorax, haemothorax, hydromediastinum, pneumothorax and pneumomediastinum.[9–11] Although the effects are less dramatic than for perforation of the heart, there is appreciable morbidity and finite mortality.[10] Hydromediastinum resulting in cardiac tamponade has been reported,[7] and perforation of the medial wall of the superior vena cava (SVC) can produce tamponade directly.[6] This is explained by the finding by Schuster and colleagues that the pericardium may ascend alongside the medial wall of the SVC by up to 5 cm (mean 3 cm).[3] Thus, placement just proximal to the atrium does not obviate the risk of tamponade.

Perforation is thought to occur as a result of mechanical trauma from the catheter tip or chemical damage from infused solutions.[12] This results in two warning signs: visceral-type chest pain on infusion of drugs or parenteral nutrition solutions[13] and a curved appearance of the distal catheter seen on chest x-ray.[9]

Factors affecting the risk of perforation by catheters (both venous and cardiac) are numerous. Stiffer catheters are more likely to perforate.[14] Stiffness is a function of the composition of the catheter (Silastic probably being safest) and the number of the lumen (a function of the greater diameter and presence of 'septa' within the catheter). The angle that the catheter tip makes with the wall of the vein or heart is crucial; both *in vitro*[14] and clinical evidence indicates that the more perpendicular the catheter to the wall, the greater the risk of perforation.[11 15] Left-sided catheters pose a particular problem because the left innominate (brachiocephalic) vein forms a near right angle to the SVC. Catheters entering the SVC from the left therefore have a tendency to impinge on the lateral wall of the SVC. The resulting increased risk of perforation is well documented.[9 11 15]

A sharp, inflexible catheter tip increases the risk of perforation, as does excessive mobility of the tip (seen with brachial catheters upon movement of the arm). Fluid infused under high pressure or at a high flow rate may increase the risk of perforation; this may occur with the use of side ports as well as end ports. When myocardial perforation does occur in this situation, the risk of tamponade is greatly increased. Finally, it is likely that some perforations are due to trauma from the guidewire or dilator, particularly when tamponade occurs early after insertion.

Thrombosis and catheter-related sepsis

The overall thrombosis rate from central venous catheterization is between 30 and 70%.[16–18] Thrombosis occurs where there has been repeated trauma to the endothelium from the catheter tip.[19] There is increasing evidence of a relationship between high placement of the catheter tip (upper SVC or above) and thrombosis.[19 20] Although most thrombosis is either asymptomatic or results in catheter blockage alone, life-threatening sequelae are probably under-recognized. The incidence of pulmonary embolism from catheter-related thrombosis may be up to 60% for both short- and long-term catheterization;[16 21 22] one study reported a mortality of 12%.[22] In addition, thrombosis of the axillary or subclavian veins can lead to significant morbidity and requires anticoagulation; SVC obstruction is possible and may be fatal.[19]

Catheter-related sepsis (CRS) is a major problem, with a direct mortality rate of 25%.[23] A clear relationship has been established between CRS and thrombosis,[16 17] and when the two combine to produce septic thrombophlebitis the result is devastating. Although it is not clear whether infection predisposes to thrombosis or *vice versa*, the morbidity and mortality that potentially originate from thrombosis due to a high-lying catheter tip (with or without infection) is enormous, and in quantitative terms may far exceed that related to cardiac tamponade.

Extravasation

Extravasation of fluid or drugs from proximal side-holes is a potentially serious complication of catheters inserted to an inadequate depth.[24]

Positioning

A major problem in correctly siting central venous catheters is the lack of reliable surface landmarks. Although some authors recommend points such as the sternal angle as being at the level of the junction of the SVC and right atrium,[11] most recommend a chest x-ray as the only practical, reliable test. Schuster and colleagues identify the carina as a radiological landmark below which the tip is likely to be within the pericardial sac.[3] However, given that the SVC is only 6 cm long and the carina is roughly 3.5 cm higher than the SVC/atrial junction, placing the tip above the carina is likely to put it in a risk area for thrombosis or, particularly for left-sided catheters, into a position at higher risk of perforation. In addition, a frontal chest radiograph does not exclude a catheter position in smaller vessels (e.g. azygos vein) or an extravascular site adjacent to the correct site.

The use of right atrial electrocardiography during insertion of central venous catheters has been claimed to be of value.[26] However, such a technique can tell the operator only whether the tip is within the atrium, not where it is within the venous system. The use of an image intensifier permits visualization of the tip position but is not available routinely. Ultrasound, although very useful for aiding insertion, is of limited value in confirming tip placement. It will show misplacement in the subclavian, axillary or

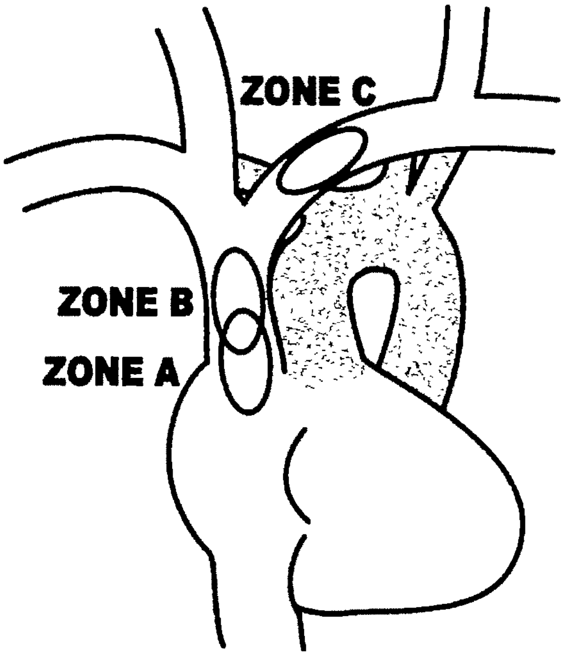

Fig 1 Stylized diagram of heart and great veins. Angles may be more acute *in vivo*

internal jugular veins but is not suitable for imaging the SVC. Venography and even computed tomography are of value in situations where the line position is in doubt and reinsertion is undesirable.

Current guidelines on tip position focus only on the risk of tamponade. We believe that an unsatisfactory tip position above the heart should not be accepted purely to satisfy these guidelines. Whenever the catheter negotiates a sharp bend, the catheter must be passed a reasonable distance beyond the bend such that the axes of the catheter and vein are aligned. In the case of insertion from the left side, this may be achievable only by siting the tip in the right atrium. Reference to a stylized diagram of the heart and great veins may provide some guidance (Fig. 1).

Zone A (low SVC/upper right atrium). This is a suitable tip site from any access point in the upper body. We believe catheter tips can be sited safely within the upper right atrium provided they do not abut the atrial wall end-on or pass through the tricuspid valve or into the coronary sinus.[6,13,20,25,26]

Zone B (upper SVC). This is a suitable site for tips of catheters placed via the right internal jugular route.[9,10]

Zone C (mid-point, left innominate vein). This is a suitable site for the tip when the catheter is introduced from the left internal jugular or subclavian vein, and reduces the risk of SVC perforation.[11]

Conclusions

The catheter tip should be placed in as large a vein as possible, ideally outside the heart and parallel with the long axis of the vein such that the tip does not abut the vein or heart wall end-on.

There are complications associated with all tip positions and a lack of good evidence on which to base practice. There is no evidence that the complications of short-term versus long-term catheterization are qualitatively different, but the event rate per patient is likely to be higher with the latter, requiring meticulous attention to detail.

Individual clinical factors must dictate the choice of access point and site of the catheter tip. Ultimately, the risks of central venous catheterization will be minimized only by clinicians having a detailed knowledge of the complications of catheterization, a high index of suspicion that clinical deterioration may be due to the catheter, and a readiness to take action. Clinicians should audit their results and be prepared to justify individual practice.

S. J. Fletcher
A. R. Bodenham
The General Infirmary at Leeds
Leeds LS1 3EX
UK

References

1 Collier PE, Blocker SH, Graff DM, Doyle P. Cardiac tamponade from central venous catheters. *Am J Surg* 1998; **176**: 212–4
2 Waghorn DJ. Intravascular device associated infection. A 2 year analysis of cases in a district general hospital. *J Hosp Infect* 1994; **28**: 91–101
3 Schuster M, Nave H, Piepenbrock S, Pabst R, Panning B. The carina as a landmark in central venous catheter placement. *Br J Anaesth* 2000; **85**: 191–3
4 Multiple-lumen central venous catheterization product [package insert]. Reading, Pennsylvania: Arrow International, 1998
5 Collier PE, Goodman GB. Cardiac tamponade caused by central venous catheter perforation of the heart: a preventable complication. *J Am Coll Surg* 1995; **181**: 459–63
6 Karnauchow PN. Cardiac tamponade from central venous catheterization. *Can Med Assoc J* 1986; **135**: 1145–7
7 Defalque RJ, Campbell C. Cardiac tamponade from central venous catheters. *Anesthesiology* 1979; **50**: 249–52
8 Phibbs B, Marriot HJL. Complications of permanent transvenous pacing. *N Engl J Med* 1985; **312**: 1428–32
9 Tocino IM, Watanabe A. Impending catheter perforation of superior vena cava: radiographic recognition. *Am J Roentgenol* 1986; **146**: 487–90
10 Duntley P, Siever J, Korwes ML, Harpel K, Heffner JE. Vascular erosion by central venous catheters. *Chest* 1992; **101**: 1633–8
11 Dailey RH. Late vascular perforations by CVP catheter tips. *J Emerg Med* 1988; **6**: 137–40
12 Flatley ME, Schapira RM. Hydromediastinum and bilateral hydropneumothorax as delayed complications of central venous catheterization *Chest* 1993; **103**: 1914–6
13 Passaro ME, Steiger E, Curtas S, Seidner DL. Long-term Silastic catheters and chest pain. *JPEN J Parenter Enteral Nutr* 1994; **18**: 240–2
14 Gravenstein N, Blackshear RH. In vitro evaluation of relative perforating potential of central venous catheters: comparison of

materials, selected models, number of lumens and angles of incidence to simulated membrane. *J Clin Monit* 1991; **7**: 1–6

15 Mukau L, Talamini MA, Sitzmann JV. Risk factors for central venous catheter-related vascular erosions. *JPEN J Parenter Enteral Nutr* 1991; **15**: 513–6

16 Timsit JF, Farkas JC, Boyer JM, *et al.* Central vein catheter-related thrombosis in intensive care patients: incidence, risk factors and relationship with catheter-related sepsis. *Chest* 1998; **114**: 207–13

17 Raad II, Luna M, Khalil SM, Costerton JW, Lam C, Bodey GP. The relationship between the thrombotic and infectious complications of central venous catheters. *JAMA* 1994; **271**: 1014–6

18 Hoch JR. Management of the complications of long-term venous access. *Semin Vasc Surg* 1997; **10**: 135–43

19 Puel V, Caudry M, Le Metayer P, *et al.* Superior vena cava thrombosis related to catheter malposition in cancer chemotherapy given through implanted ports. *Cancer* 1993; **72**: 2248–52

20 Stanislav GV, Fitzgibbons RJ, Bailey RT, Mailliard JA, Johnson S, Feole JB. Reliability of implantable central venous access devices in patients with cancer. *Arch Surg* 1987; **122**: 1280–3

21 Pollard AJ, Sreeram N, Wright JG, Beath SV, Booth IW, Kelly DA. ECG and echocardiographic diagnosis of pulmonary thromboembolism associated with central venous lines. *Arch Dis Child* 1995; **73**: 147–50

22 Dollery CM, Sullivan ID, Bauraind O, Bull C, Milla PJ. Thrombosis and embolism in long-term central venous access for parenteral nutrition. *Lancet* 1994; **344**: 1043–5

23 Pittet D. Nosocomial bloodstream infections in the critically ill. *JAMA* 1994; **272**: 1819–20

24 Chalkiadis GA, Gouke CR. Depth of central venous catheter insertion in adults: an audit and assessment of a technique to improve tip position. *Anaesth Intens Care* 1998; **26**: 61–6

25 Taber SW, Bergamini TM. Long-term venous access: indications and choice of site and catheter. *Semin Vasc Surg* 1997; **10**: 130–4

26 McGee WT, Ackermann BL, Rouben LR, Prasad VM, Bandi V, Mallory DL. Accurate placement of central venous catheters: a prospective, randomized, multicenter trial. *Crit Care Med* 1993; **21**: 1118–23

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CLINICAL INVESTIGATIONS

The carina as a landmark in central venous catheter placement†

M. Schuster[1], H. Nave[2], S. Piepenbrock[1], R. Pabst[2] and B. Panning[1*]

[1]Department of Anaesthesiology and [2]Department of Anatomy, Medical School Hannover,
D-30623 Hannover, Germany
**Corresponding author*

Location of the tip of a central venous catheter (CVC) within the pericardium has been associated with potentially lethal cardiac tamponade. Because the pericardium cannot be seen on chest x-ray (CXR), an alternative radiographic marker is needed for correct placement of CVCs. The anatomy of the region was studied in 34 cadavers. The carina was a mean (SEM) distance of 0.4 (0.1) cm above the pericardial sac as it transverses the superior vena cava (SVC). In no case was the carina located below the pericardial sac. The carina is a reliable, simple anatomical landmark for the correct placement of CVCs. In almost all cases, the carina is radiologically visible even in poor quality, portable CXRs. CVC tips should be located in the SVC above the level of the carina in order to avoid cardiac tamponade.

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Cardiac tamponade is a life-threatening complication of central venous catheter (CVC) placement. Current guidelines strongly advise that the CVC tip lies in the superior vena cava (SVC) and outside the pericardial sac.[1] This is difficult to achieve as the exact location of the pericardium cannot be seen on a normal chest x-ray (CXR). Various radiographic landmarks have been described to ensure extrapericardial location of the CVC tip in a safe position,[2–4] but none of these has achieved general acceptance. In addition, the awareness of physicians regarding the risks of malpositioned CVCs is still limited.[4]

We are unaware of any anatomical studies to verify the exact location of the pericardial sac in relation to other radiographically visible anatomical structures. Some clinicians use the carina as a landmark for the correct location of CVC tips, but this has not been investigated systematically. The aim of our study was to determine whether the carina can be used as a landmark below which no catheter tip should be located.

Material and methods

Thirty-four cadavers [11 male, 23 female, mean age 78 ((SEM) 1.7) (range 49–98) yr; length 166 (1.7) cm, range 144–186 cm] which were used for first year medical students were examined in the dissecting room. After opening the chest, the lungs were removed by cutting the main bronchi and the accompanying vessels ~5 cm distal to the carina. The pericardial sac was cut open with a lambda-shaped wide incision. The aorta, the superior and inferior vena cava, and the pulmonary trunk were cut in the intrapericardial section of the vessels 2–3 cm away from the heart, so that the heart could be removed. The anatomy of the pericardial sac and its reflection were preserved with great care. The carina, located medially and posteriorly to the level of the great vessels, was palpated after removal of the heart. The sagittal distance was measured between the middle of the carina and the middle of the SVC.

In this university hospital with 1400 beds, several thousand CVCs are inserted each year. To assess whether the carina is visible in CXRs taken in the intensive care units, we studied 100 consecutive newly placed CVCs in seven intensive care units (cardiac surgery, abdominal surgery, transplantation surgery, trauma, anaesthesiology, cardiology and respiratory). All CXRs were taken as portable antero-posterior CXRs with the patient lying supine.

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†This article is accompanied by Editorial II

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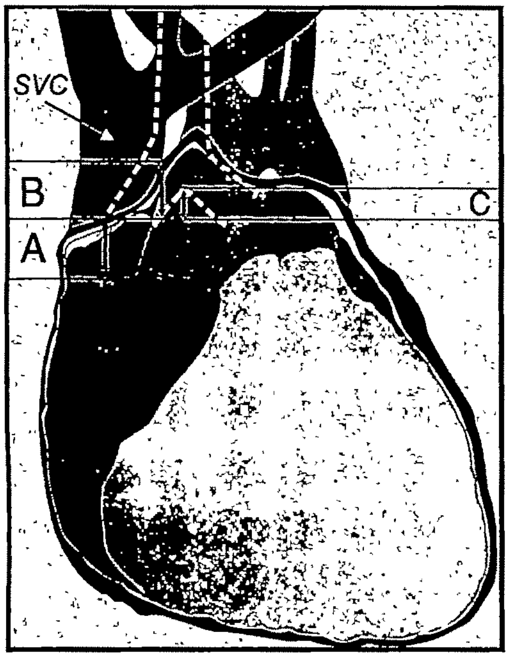

Fig 1 The heart, the great vessels and the pericardial sac. The carina, which is anatomically located dorsally to the view shown, is indicated by dotted lines The pericardial sac is depicted in black and white around the heart. All numbers are arithmetic mean (SEM) (A) The intrapericardial part of the SVC (3.0 (0.2) cm, range 1.0–5.0 cm) (B) The medial side of the SVC where a duplication of the pericardium fortifies the vessel wall (2.4 (0.1) cm, range 1.6–4.0 cm) (C) The longitudinal distance between the carina and the pericardium as it transverses the SVC (0.4 (0.1) cm; range 0.0–2.1 cm). SVC denotes superior vena cava.

Results

The pericardium transverses the SVC almost horizontally (Fig. 1). At the medial side of the SVC, the pericardium is attached to the SVC wall and ascends with the SVC (Fig. 1) up to the beginning of the aortic arch. It then leaves the SVC and follows the aortic arch. The carina was a mean (SEM) distance of 0.4 (0.1) cm (range 0.0–2.1 cm) above the pericardium as it transverses the SVC (Fig. 1). The distance did not correlate with the length of the patient. In no case was the carina located below the pericardial reflection. The intrapericardial part of the SVC was 3.0 (0.2) cm (range 1.0–5.0 cm) long. The sagittal distance of the carina to the middle of the SVC was 3.0 (0.1) cm (range 1.5–4.1 cm).

Reviewing the post-insertion CXRs, we found that the carina could be identified in 96%. In 58% the catheter tip was located below the carina.

Discussion

Since the first report in 1956,[5] cardiac tamponade following CVC placement has been reported in patients of all ages and with different types of catheters.[1 6 7] The mortality from cardiac tamponade following CVC placement was very high in all the series,[1 8 9] but the real incidence is unknown. However, it is likely that this condition is under-reported.[4 8] In recent years, there have been modifications in catheters to reduce the risk of catheter-induced perforation, but there is no evidence that these new catheters reduce the incidence of cardiac tamponade.[4] Indeed, there are several reports of cardiac tamponade caused by soft silastic CVCs.[1 10 11]

To prevent cardiac tamponade, various safe location criteria have been suggested, but all have major drawbacks Greenall and colleagues suggested that the catheter tip should be no more than 2 cm inferior to a line drawn between the lower borders of the clavicles on an erect posterior-anterior CXR.[2] However, in the portable antero-posterior CXR used in intensive care units with the patient lying supine, the film is located much closer to the beam source than in posterior-anterior CXRs taken with the patient standing upright. As a consequence, anatomical structures located anteriorly and more peripherally, such as the clavicles, can be augmented on the film by more than 20%. This parallax effect makes the criteria suggested by Greenall less reliable. To circumvent the parallax problem, Rutherford and colleagues suggested that the angle formed between the right main bronchus and the trachea, which is located closer to the SVC, is a more appropriate landmark.[3] However, their work was not based on anatomical studies and it remained unclear whether it really guarantees an extrapericardial location of the CVC tip. Collier and colleagues suggested avoiding any location of the CVC tip which can be seen inside the cardiac silhouette on CXR,[4] but the border between the SVC and the right atrium is often indeterminable on CXRs. Moreover, the cardiac silhouette does not match the anatomical location of the pericardial sac, as our data show that the intrapericardial part of the SVC is 3.0 (0.2) cm (range 1.0–5.0 cm). A correctly placed catheter according to the criterion suggested by Collier and colleagues could still cause a cardiac tamponade by vascular erosion of the intrapericardial SVC, which has been reported previously.[8 12]

Our study shows that the carina is a reliable landmark for the placement of CVCs. In all cases, the pericardial sac ends below the level of the carina. The longitudinal distance between the level of the carina and the level of the upper end of the pericardial sac has a relatively small variability and does not correlate with the length of the patient. Our study also explains why CVC tips abutting the lateral wall of the SVC are especially dangerous:[13] the lateral side of the SVC is much weaker than the medial side, where the pericardial sac fortifies the vessel wall.

The carina as an anatomical landmark has several advantages; due to its fixation with connective tissue, its location is preserved even in pulmonary pathology. The central location and the small sagittal distance between it and the SVC (range 1.5–4.1 cm in our study) limit any parallax effect. Most importantly, the carina is easily visible even in a poor quality portable antero-posterior CXR.

In conclusion, cardiac tamponade is a potentially life-threatening complication of CVC placement which can be avoided if all catheter tips are located above the carina on CXR.

References

1 Collier PE, Blocker SH, Graff DM, Doyle P. Cardiac tamponade from central venous catheters. *Am J Surg* 1998; **176**: 212–4

2 Greenall MJ, Blewitt RW, McMahon MJ. Cardiac tamponade and central venous catheters. *BMJ* 1975; **2**: 595–7

3 Rutherford JS, Merry AF, Occleshaw CJ. Depth of central venous catheterization: an audit of practice in a cardiac surgical unit. *Anaesth Intens Care* 1994; **22**: 267–71

4 Collier PE, Goodman GB. Cardiac tamponade caused by central venous catheter perforation of the heart: a preventable complication. *J Am Coll Surg* 1995; **181**: 459–63

5 Brown CA, Kent A. Perforation of right ventricle by polyethylene catheter. *South Med J* 1956; **49**: 466–7

6 Engelenburg KCA, Festen C. Cardia tamponade: a rare but life-threatening complication of central venous catheters in children. *J Pediatr Surg* 1998; **33**: 1822–4

7 Murray BH, Cohle SD, Davison P. Pericardial tamponade and death from Hickman catheter perforation. *Am Surg* 1996; **62**: 994–7

8 Defalque RJ, Campbell C. Cardiac tamponade from central venous catheters. *Anesthesiology* 1979; **50**: 249–52

9 Karnauchow PN. Cardia tamponade from central venous catheterization. *Can Med Assoc J* 1986; **135**: 1145–7

10 Greenspoon JS, Masaki DI, Kurz CR. Cardiac tamponade in pregnancy during central hyperalimentation. *Obstet Gynecol* 1989; **73**: 465–6

11 Kalen V, Medige TA, Rinsky LA. Pericardial tamponade secondary to perforation by central venous catheters in orthopaedic patients. *J Bone Joint Surg* 1991; **73**: 1503–6

12 Aldridge H, Jay A. Central venous catheters and heart perforation. *Can Med Assoc J* 1986; **135**: 1083–4

13 Ellis LM, Vogel SB, Copeland EM. Central venous catheter vascular erosions. *Ann Surg* 1989; **209**: 475–8

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Serum mitochondrial aspartate transaminase activity after isoflurane or halothane anaesthesia

J. R. Darling[1*], P. C. Sharpe[2], E. K. Stiby[1], J. A. McAteer[1], G. P. R. Archbold[2] and K. R. Milligan[1]

[1]*Department of Anaesthesia, Musgrave Park Hospital, Belfast BT9 7JB, UK.* [2]*Department of Clinical Chemistry, Belfast City Hospital, Belfast BT9 7AB, UK*

**Corresponding author*

We examined the effect of halothane or isoflurane anaesthesia on hepatic function in 30 ASA I–III patients aged 18–70 yr undergoing lumbar discectomy. Hepatic function was assessed before anaesthesia, at the end of surgery, and at 3, 6, 24 and 48 h after surgery using routine enzyme tests of hepatic function and mitochondrial aspartate transaminase (mAST) activity. Although serum mAST activities increased after surgery in both groups of patients, these increases were statistically significantly greater in the group that received halothane. The groups were similar with regard to other tests of hepatic function. Calculation of the ratio of serum enzyme activities compared to baseline values suggested that mAST is a sensitive marker of anaesthetic-induced hepatic injury.

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Aspartate transaminase (AST) consists of two genetically distinct, structurally different isoenzymes known as mitochondrial and soluble (or cytosolic) AST. The plasma concentration of mitochondrial AST (mAST) is small (normal <4 u litre^{-1}) despite its considerable activity in heart and liver tissues.[1] mAST probably has a shorter half-life than cytosolic AST and makes up 80% of the total AST in liver tissue. It has been suggested that mAST is preferentially located in the perivenous hepatocytes which are more susceptible to damage by both alcohol and anoxia.[2 3] Serum concentrations of mAST may be measured immunochemically and could be a marker of damage resulting from anaesthetic agents such as halothane.[4]

We compared the effect of halothane and isoflurane anaesthesia on serum mAST to determine if serum mAST is a more sensitive marker for anaesthetic-induced liver damage than AST, alanine transaminase (ALT), alkaline phosphate (ALP), γ-glutamyl transferase (γGT) and serum bilirubin.

Patients and methods

With written informed consent and University Ethics Committee approval, 30 ASA grade I–III patients undergoing lumbar discectomy were enrolled in the study. All patients were aged 18–70 yr and had no history of hepatic disease or recent heavy alcohol intake (>21 u weekly for men and >14 u weekly for women). Any patient who had a general anaesthetic in the previous 6 months was excluded from the study.

Anaesthesia and analgesia

Patients were randomly allocated to receive either halothane or isoflurane by opening sealed envelopes after enrolment into the study. Premedication consisted of temazepam (20 mg) in all cases. Anaesthesia was induced with thiopentone (5 mg kg^{-1}) and intubation of the trachea was facilitated with atracurium (0.5 mg kg^{-1}). Analgesia was provided by morphine (10 mg) at induction and droperidol (2.5 mg) was administered intravenously as an anti-emetic. Patients were ventilated to maintain their end-tidal carbon dioxide concentration at 4.6–5.9 kPa, and placed in a modified tuck position for surgery.[5] Patients in the halothane and isoflurane groups received halothane and isoflurane, respectively, in nitrous oxide and oxygen ($F\text{I}_{\text{O}_2}$=0.4). Initial expired concentrations of anaesthetic agent were 1.0 MAC that was reduced if systolic arterial pressure decreased by more than 30% of baseline values. Fluid therapy was Dextran 70 in 0.9% saline (500 ml) followed by Hartmann's solution as required during surgery, and 0.18% saline in 4% dextrose (100 ml h^{-1})

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after anaesthesia. Heart rate and rhythm, non-invasive arterial pressure and peripheral oxygen saturation by pulse oximeter were monitored throughout anaesthesia. End-tidal carbon dioxide and anaesthetic concentrations were also recorded during anaesthesia. Bupivacaine 0.25% (20 ml) was applied to the wound before it was sutured and neuromuscular blockade reversed with neostigmine 2.5 mg and glycopyrrolate 0.5 mg. Postoperative analgesia consisted of patient-controlled analgesia (morphine sulphate: 1 mg bolus and 5 min lock-out).

Laboratory analysis

Venous blood samples were drawn immediately before induction of anaesthesia, at the end of surgery (time 0), and 3, 6, 24 and 48 h later. The samples were centrifuged and the serum assayed for bilirubin concentration and activities of creatine kinase (CK), ALT, ALP, γGT and AST using a multi-channel analyser (Prisma, Clinicon-AB). The remaining serum was stored at –20°C and assayed for mAST at a later date by an immunochemical method.[4] Rabbit antibodies against human soluble AST were added to the serum in the presence of polyethylene glycol and the sample was centrifuged to precipitate the soluble AST. Residual mAST in the supernatant was then assayed in the presence of exogenous pyridoxal phosphate by coupling oxaloacetate production with NADH in reaction with malate dehydrogenase (absorbance change monitored at 340 nm (Prisma, Clinicon-AB)). The detection limit of the assay was less than 0.5 u litre^{-1} and the coefficient of variation was less than 3% of the residual mAST.

Table 1 Details of patients studied (median (range))

	Halothane (*n*=15)	**Isoflurane (*n*=15)**
Age (yr)	42 (24–56)	41 (31–69)
Weight (kg)	70 (55–105)	75 (58–103)
Gender (M/F)	9/6	11/4
Alcohol intake (u week^{-1})	4 (0–20)	7 (0–16)
Tylex (*n* day^{-1})	7	5
Diazepam (*n* day^{-1})	3	4
Diclofenac (*n* day^{-1})	4	3
Duration of hypotension (min)	60 (55–135)	63 (60–110)
Dose (MAC h^{-1})	1.4 (0.7–3.5)	1.4 (0.61–1.8)
Lowest systolic ABP (mm Hg)	95 (79–124)	100 (69–127)
Lowest diastolic ABP (mm Hg)	55 (40–71)	58 (40–65)

Data were analysed using Wilcoxon ranked pairs within groups and Mann–Whitney *U*-test between groups. Ratios of enzyme activities compared to baseline values were calculated and analysed between groups using the Mann–Whitney *U*-test.

Results

Fifteen patients were anaesthetized with isoflurane and 15 received halothane. The groups were similar in age, weight, gender, alcohol intake, duration of hypotension, minimum arterial pressure and dose of anaesthesia (Table 1). All patients had liver function test values of less than twice the upper limit of the reference range prior to anaesthesia. In both groups, serum concentration of bilirubin increased significantly above baseline at 24 and 48 h after anaesthesia (Table 2). Serum ALT activity decreased significantly ($P<0.05$) below baseline throughout the study period in the halothane group (Table 2). ALP and γGT activities significantly ($P<0.05$) decreased from baseline in both groups at the end of anaesthesia and in the case of γGT

Table 2 Serum bilirubin concentrations (μmol litre^{-1}) and enzyme activities (u litre^{-1}) for the groups receiving halothane (H) and isoflurane (I). Median (1st, 3rd quartiles). **P*<0.05 difference from baseline activity (Wilcoxon rank sum)

Test (ref. range)		Baseline	**Time after surgery (h)**				
			0	**3**	**6**	**24**	**48**
Bilirubin (3–17)	H	10 (7,15)	11 (7,13)	10 (7,11)	11 (8,14)	17* (10,22)	13* (10,19)
	I	10 (7,15)	11 (8,16)	10 (8,14)	11 (8,14)	15* (13, 24)	14* (11,19)
ALT (10–40)	H	35 (14,55)	29* (12,44)	28* (11,42)	29* (13,45)	24* (14,38)	22* (15,38)
	I	21 (13,28)	17* (12,25)	17 (11,24)	18 (11,26)	16 (13,26)	23 (15,30)
ALP (90–280)	H	167 (145,189)	131* (116,170)	128* (116,160)	140* (123,163)	153 (141,183)	172 (144,188)
	I	144 (130,186)	135* (98,162)	143 (125,159)	146 (129,165)	164 (141,195)	169 (144,191)
γGT (5–60)	H	36 (16,56)	26* (14,55)	23* (13,43)	26* (13,43)	25* (16,48)	27* (18,41)
	I	26 (15,34)	21* (113,27)	22 (14,28)	20* (16,24)	22* (17,25)	22 (20,39)
CK (50–150)	H	74 (55,123)	73 (55,122)	76 (57,114)	69 (52,112)	72 (54,113)	69 (44,124)
	I	89 (66,123)	88 (67,113)	89 (65,111)	99 (60,119)	92 (59,117)	87 (60,115)

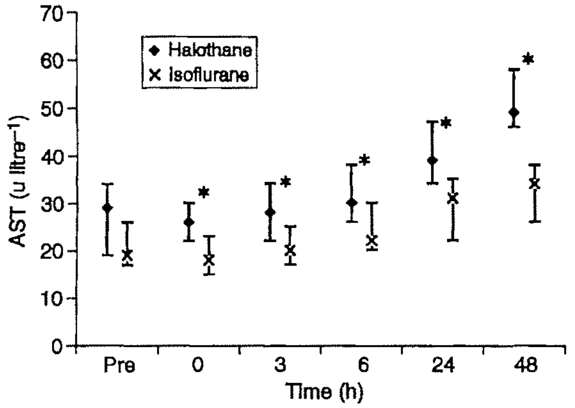

Fig 1 Serum aspartate transaminase (AST) activity (u litre^{-1}) before and after halothane or isoflurane anaesthesia. Values are median and interquartile range. Normal range: 17–45 u litre^{-1}. *$P<0.05$ difference between groups using Mann–Whitney *U*-test

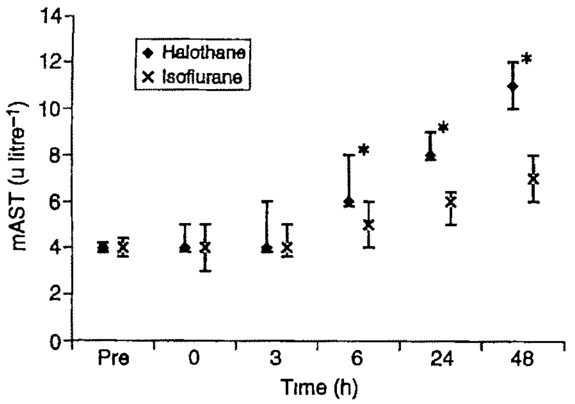

Fig 2 Serum mitochondrial aspartate transaminase (mAST) activity (u litre^{-1}) before and after halothane or isoflurane anaesthesia. Values are median and interquartile range. Normal range 2–4 u litre^{-1}. *$P<0.05$ difference between groups using Mann–Whitney *U*-test

remained below baseline activities throughout the study period (Table 2).

Serum AST and mAST activity increased throughout the study period in both groups (Figs 1 and 2). In the halothane group this increase in serum activity reached significance in blood samples taken at more than 6 h after anaesthesia for AST and in all postoperative samples for mAST. In the isoflurane group, the increase in both AST and mAST reached significance at 24 and 48 h after anaesthesia.

The groups were statistically different ($P<0.05$) with regard to AST in all samples taken after operation (Fig. 1). This difference was maximal ($P<0.001$) at 48 h after operation. The groups were also statistically different with regard to mAST activity in all samples taken after 6 h (Fig. 2). This difference was maximal ($P<0.0001$) at 48 h after anaesthesia. No significant difference was noted between the groups with regard to any of the other tests of hepatic function.

The baseline activity of AST and ALT was greater in the halothane group before operation. Although this did not reach statistical significance ($P<0.05$, Fig. 1), it was felt necessary to compare the change in the activities of AST and mAST from baseline activities. There was no statistical difference between the halothane and isoflurane groups when the increase in AST was considered as a ratio (Fig. 3). When a similar plot was carried out for the ratio of mAST activity to baseline (Fig. 4), there remained a statistical difference ($P<0.001$) between the halothane and isoflurane groups at 6, 24 and 48 h after surgery.

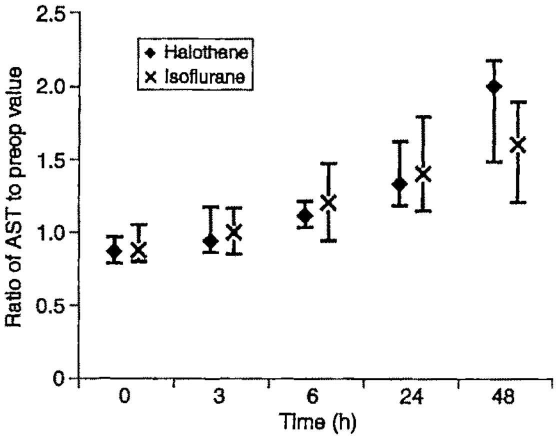

Fig 3 Ratio of serum aspartate transaminase (AST) activity after halothane or isoflurane anaesthesia to baseline activity. Values are median and interquartile range.

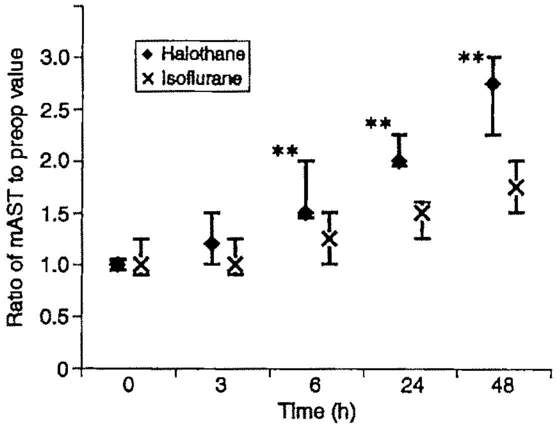

Fig 4 Ratio of serum aspartate transaminase (AST) activity after halothane or isoflurane anaesthesia to baseline activity. Values are median and interquartile range. **$P<0.001$ difference between groups using Mann–Whitney *U*-test

Discussion

These data show an increase in serum activity of both AST and mAST in patients after lumbar discectomy. This increase is significantly greater after anaesthesia with halothane than isoflurane and is in agreement with previous work that found an increase in serum concentrations of glutathione S-transferase (GST) after a single, brief exposure to halothane.[6] The conclusion of these previous studies suggested a loss of hepatocellular integrity following halothane, whereas isoflurane is free of this effect.[7]

Serum AST activity increased significantly from baseline for all samples drawn more than 6 h after surgery in the halothane group and 24 h after surgery in the isoflurane group. Serum AST activity was non-significantly greater in the halothane group prior to anaesthesia or surgery (P=0.09). Although the difference between the groups was significant (P<0.05) in all of the postoperative samples, we aimed to reduce the influence of the baseline difference by expressing the activities of AST after surgery and anaesthesia as a ratio of baseline activity (Fig. 3). This ratio did not show a statistical difference between the groups at any time after surgery, and therefore these data do not support the use of serum AST activity as an indicator of subclinical hepatic injury found after halothane anaesthesia. Other studies have provided conflicting data on the value of serum AST as an indicator of hepatic injury following halothane anaesthesia. The surgical procedure performed may be important as it has been found that serum AST activity decreases significantly after body surface or minimally invasive surgery,[8] but is significantly increased after gastric or biliary surgery.[9]

There was no difference between the groups before surgery in terms of serum mAST activity. However, after anaesthesia and surgery, serum mAST was significantly greater in the halothane group of patients (Fig. 2). A similar pattern was found when mAST activities after anaesthesia were expressed as ratios of baseline activity (Fig. 4).

Many of the patients in this study were receiving medication, including Tylex™ (paracetamol 500 mg and codeine phosphate 30 mg), diazepam and diclofenac that may cause some hepatic injury. The position of the patient during surgery may also be important because posture alters total hepatic blood flow and blood flow through the portal vein in particular.[10] The tuck position may reduce blood flow through the portal vein. The hepatic arterial response to reduced portal venous blood flow is abolished in rats anaesthetized with halothane, but maintained in the presence of isoflurane.[11] Therefore, a reduction in blood flow through the portal vein may be compensated in the isoflurane group but not in the halothane group. Patients undergoing more minor superficial surgery in the supine position may therefore allow a clearer examination of differences in liver function related to choice of anaesthetic agent.

The source of AST and mAST is not clear as both are found in liver, heart, kidney, brain and skeletal muscle.[12] It may therefore be possible that the leakage of enzyme into the serum came from muscle damage at the time of surgery.[9 13] However, the changes in serum bilirubin concentration and CK activity were similar in both groups of patients indicating similar severity of surgical tissue damage. As both groups of patients were similar in all other ways, it is most likely that the increased serum activities of mAST are due to the anaesthetic agents used and are hepatic in origin. Therefore, this study provides further evidence that a short exposure to halothane results in a greater loss of liver cell integrity than similar exposure to isoflurane.

In summary, mAST indicates hepatic dysfunction after anaesthesia with halothane. Limitations of the assay for mAST include a lack of organ specificity and the labour-intensive nature of the assay. However, the assay may become much easier in the future as automated techniques utilizing proteinases which inactivate cytosolic AST but have no effect on mAST become available.[14] Although the use of halothane is diminishing in the western world, this assay may be useful in evaluating the effects of newer anaesthetic agents on hepatic function.

Acknowledgement

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References

1 Rej R. Aspartate aminotransferase activity and isoenzyme proportions in human liver tissues. *Clin Chem* 1978; **24**: 1971–9

2 Lumeng L. New diagnostic markers of alcohol abuse. *Hepatology* 1986; **6**: 742–5

3 Sharpe PC, McBride R, Archbold GPR. Biochemical markers of alcohol abuse. *Q J Med* 1996; **89**: 137–44

4 Rej R. An immunochemical procedure for determination of mitochondrial aspartate aminotransferase in human serum. *Clin Chem* 1980; **26**: 1694–700

5 Wayne SJ. A modification of the tuck position for lumbar spine surgery· a 15-year follow-up study. *Clin Orthopaedics* 1984; **184**: 212–6

6 Allan LG, Hussey AJ, Howie J, Beckett GJ, Smith AF, Hayes JD, Drummond GB. Hepatic glutathione S-transferase release after halothane anaesthesia: open randomised comparison with isoflurane. *Lancet* 1987; **i**: 771–4

7 Hussey AJ, Aldridge LM, Paul D, Ray DC, Beckett GJ, Allan LG. Plasma glutathione S-transferase concentration as a measure of hepatocellular integrity following a single general anaesthetic with halothane, enflurane or isoflurane. *Br J Anaesth* 1988; **60**: 130–5

8 Darling JR, Murray JM, McBride DR, Trinick TR, Fee JPH. Serum glutathione S-transferase concentrations and creatinine clearance after sevoflurane anaesthesia. *Anaesthesia* 1997; **52**: 121–6

9 Clarke RSJ, Doggart JR, Lavery T. Changes in liver function after different types of surgery. *Br J Anaesth* 1976; **48**: 119–28

10 Brown HS, Halliwell M, Qamar M, Read AE, Evans JM, Wells PNT. Measurement of normal portal venous blood flow by Doppler ultrasound. *Gut* 1989; **30**: 503–9

11 Gelman S, Fowler KC, Smith LR. Liver circulation and function during isoflurane and halothane anaesthesia. *Anesth Analges* 1984; **61**: 726–30

12 Sada E, Tashiro S, Morino Y. The significance of serum mitochondrial aspartate transaminase activity in obstructive jaundice: experimental and clinical studies. *Jpn J Surg* 1990; **20**: 392–405

13 Panteghini M, Malchiodi A, Calarco M, Bonora R. Clinical and diagnostic significance of aspartate aminotransferase isoenzymes in sera of patients with liver diseases. *J Clin Chem Clin Biochem* 1984; **22**: 153–8

14 Watazu Y, Okabe H, Sugiuchi H, Uji Y, Shirashe Y, Kaneda N. Proteolytic measurement of mitochondrial aspartate aminotransferases in human serum. *Clin Biochem* 1990; **23**: 127–30

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Low-dose remifentanil increases regional cerebral blood flow and regional cerebral blood volume, but decreases regional mean transit time and regional cerebrovascular resistance in volunteers

I. H. Lorenz[1]*, C. Kolbitsch[1], M. Schocke[2], C. Kremser[2], F. Zschiegner[1], M. Hinteregger[1], S. Felber[2], C. Hörmann[1] and A. Benzer[1]

[1]*Department of Anesthesia and Intensive Care Medicine and* [2]*Department of Magnetic Resonance Imaging, University of Innsbruck, Innsbruck A-6020, Austria*

**Corresponding author*

We have used contrast media-enhanced perfusion magnetic resonance imaging MRI to measure regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV), regional mean transit time (rMTT) and regional cerebrovascular resistance (rCVR) in volunteers at baseline and during infusion of remifentanil (0.1 μg kg^{-1} min^{-1}). Remifentanil increased rCBF and rCBV in white and grey matter (striatal, thalamic, occipital, parietal, frontal) regions, with a parallel decrease in rMTT in those regions with the exception of occipital grey matter. rCVR was decreased in all regions studied. The relative increase in rCBF was greater than that in rCBV. Cerebral haemodynamics were increased significantly in areas less rich in μ-opioid receptors with a tendency towards more pronounced increases in rCBF and rCBV in pain-processing areas. Furthermore, interhemispheric differences in rCBF, rCBV and rMTT found prior to drug administration were almost eliminated during infusion of remifentanil. We conclude that, apart from direct and indirect cerebrovascular effects of remifentanil, these findings are consistent with cerebral excitement and/or disinhibition.

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Keywords: brain, blood flow; brain, cortex, cerebral; blood, volume; measurement techniques, nuclear magnetic resonance; analgesics opioid, remifentanil

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Introduction

Remifentanil is an ultrashort-acting, potent and selective μ-opioid receptor agonist.[1–4] Because μ-opioid receptors have been found to be present in nociceptive and sensorimotor-integrative regions of the central nervous system[5–8] and are involved in regulating cerebral haemodynamics,[9–12] the effect of opioids on cerebral haemodynamics may have regional differences.

In a positron emission tomography (PET) study, remifentanil modulated human cerebral blood flow (CBF) in a regionally specific fashion with increases in areas associated with pain processing.[13] However, that study showed only relative changes in regional cerebral blood flow (rCBF).

PET studies are known to suffer from a lack of anatomical resolution.[14 15] Thus, the present study used contrast media-enhanced magnetic resonance imaging (MRI) perfusion measurements to determine the influence of remifentanil on rCBF, regional cerebral blood volume (rCBV),[16] regional mean transit time (rMTT) and regional cerebrovascular resistance (rCVR)[17] in volunteers

Methods

After obtaining the approval of the local University Ethics Committee and written informed consent, 10 healthy, male volunteers, who had no history of drug use or abuse and no history of surgery in the previous 6 months, underwent physical examination and blood screening for opioids. Following negative drug screening and a 6-h fasting period on the day of the experiment, subjects underwent two consecutive MRI measurements of contrast media-enhanced cerebral perfusion.

Wearing a tightly fitting face mask the volunteers breathed normally (end-tidal carbon dioxide concentration (Et_{CO_2})=40 mm Hg) at an inspired oxygen fraction (FI_{O_2}) of 0.5. The volunteers had been trained by both verbal instruction and by watching the capnographic trace of the monitor on the day prior to the MRI session. During the

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experiment, breathing at a constant Et_{CO_2} (e.g. 40 mm Hg) was supported by voice command when necessary.

Following baseline measurement, a continuous infusion of remifentanil (0.1 μg kg^{-1} min^{-1}) was started. The continuous infusion rate for steady-state[18 19] was preceded by a 25% increased infusion rate for a period of 5 min. After 10 min of remifentanil infusion, tests of thermal and tactile nociception as well as of pupillary reflex were repeated to verify opioid action before starting MRI measurement. Cumulative duration of remifentanil infusion was 45–60 min.

A dose reduction of 25% was performed when side effects occurred (e.g.: Sp_{O_2} <93%; respiration rate <5 b.p.m.; no reaction to verbal commands or nausea and vomiting).

FI_{O_2}, Et_{CO_2}, non-invasive mean arterial pressure (MAP), electrocardiogram (ECG), respiration frequency (RF) and haemoglobin oxygen saturation (Sp_{O_2}) were monitored during the investigation (Compact Datex®, Finland).

MRI measurements were performed on a 1.5-Tesla whole-body scanner (Magnetom VISION, Siemens, Germany) using a standard circular polarized head coil. Single-shot echo planar imaging (EPI) was performed with a repetition time (TR) of 2 s and an echo time (TE) of 64 ms. An acquisition matrix of 64×128 (FOV 22×22 cm, inplane resolution 1.6×1.6 mm) was used. The slice thickness was set to 5 mm and 15 slices were measured simultaneously. A paramagnetic contrast agent Gd-DTPA (0.1 mmol kg^{-1}) was injected into an antecubital vein at a rate of 9 ml s^{-1} using an MR-compatible power-injector (SPECTRIS, Medrad, Pittsburgh, PA, USA). Echo-planar-imaging scans (*n*=60) were performed at 2-s intervals to cover the whole passage of the contrast agent through the brain.

CBV and CBF were calculated in regions of interest (ROIs) placed bilaterally in corresponding white matter and in frontal, parietal, occipital, thalamic and striatal grey matter.

The basic concept used to determine CBV and CBF was previously described by Ostergaard and colleagues.[16] CBF values are given in (ml 100 ml^{-1} min^{-1}) and CBV values in (ml 100 ml^{-1}).

The mean transit time, which defines the average time that any particle of tracer, such as contrast media, remains within the region of interest,[20] was calculated according to the equation:

$$MTT = \frac{CBV}{CBF} \times 60 \qquad (1)$$

MTT is given in s.

Cerebrovascular resistance (CVR) was calculated with the equation:[17]

$$CVR = \frac{MAP}{CBF} \qquad (2)$$

CVR is given in 10^4 N m^{-2} min 100 ml^{-1}.

Statistical analysis

Data are presented as mean (SEM) and mean (SD) and were tested for normal distribution with the Kolmogorov–Smirnov test. In the case of normal distribution, analysis of variance (ANOVA) for repeated measurements with Bonferroni correction for multiple testing was performed. Otherwise, the Mann–Whitney *U*-test or Kruskal–Wallis test was employed. $P<0.05$ was considered statistically significant. The statistical computer package SPSS ® 8.0. for Windows (95) run on a Compaq ® Deskpro EP Series 6350/6.4 was used for statistical analysis.

Results

All volunteers (*n*=10; age range 20–28 yr, weight: 76 (SD) (6) kg; height: 181 (6) cm) completed the study without complications. All were right-handed males of ASA physical status I and non-smokers. Body weight in all volunteers was within 10% of ideal body weight.

Heart rate significantly decreased during remifentanil infusion (baseline: 67 (13) beats min^{-1} *vs* remifentanil: 61 (14) beats min^{-1}). In contrast, mean arterial pressure, RF, Sp_{O_2} and Et_{CO_2} remained unchanged during infusion of remifentanil (Table 1).

Opioid side effects observed are summarized in Table 2. The average cumulative dose of remifentanil administered was 228 (41) μg.

Table 1 Haemodynamic and respiratory values HR, heart rate, MAP, mean arterial pressure, Sp_{O_2}, pulsoxymetrically measured haemoglobin oxygen saturation; Et_{CO_2}, end-tidal CO_2 concentration; RF, respiration frequency. *Significant to baseline $P<0.05$. Values are given as mean (SD)

n=10	HR (beats min^{-1})	MAP (mm Hg)	Sp_{O_2} (%)	Et_{CO_2} (mm Hg)	RF (b.p.m)
Baseline	67 (13)	90 (7)	99 (1)	40 (0.7)	10 (4)
Remifentanil (0.1 μg kg^{-1} min^{-1})	61 (14)*	90 (7)	99 (1)	40 (0.3)	10 (5)

rCBF

At baseline grey matter rCBF ranged from 127.0 (SEM) (1.10) to 149.1 (1.2) ml 100 ml^{-1} min^{-1}, whereas white matter rCBF was 57.0 (0.4) ml 100 ml^{-1} min^{-1} (Table 3, Fig. 1). During remifentanil infusion, rCBF increased in all regions studied. This increase in rCBF was less pronounced in white compared with grey matter regions, except for the left-hemispheric parietal grey matter. rCBF increased most in bilateral striatal grey matter as well as in right thalamic and left occipital grey matter (Table 3).

At baseline, left-to-right interhemispheric differences in rCBF were present in all regions with the exception of thalamic grey matter (Fig. 1). Left-hemispheric striatal and frontal grey matter showed a higher rCBF than did the right-hemispheric areas. In contrast, in left-hemispheric parietal and occipital grey and white matter, rCBF was lower than in corresponding right-hemispheric areas. During remifentanil infusion, interhemispheric differences were eliminated except for the parietal grey matter, where left-hemispheric rCBF remained lower than right-hemispheric (Table 3, Fig. 2).

Table 2 Synopsis of side effects observed during remifentanil infusion in volunteers (n=10)

Sensation of warmth	10 (10)
Pupil constriction after 5 min	10 (10)
Comfortable	5 (10)
Skin itching	4 (10)
Dreams	2 (10)
Dry mouth	2 (10)
Flushing	1 (10)
Feeling of tightness in the chest	1 (10)
Queasy feeling	0 (10)
Sweating	0 (10)
Vomiting	0 (10)

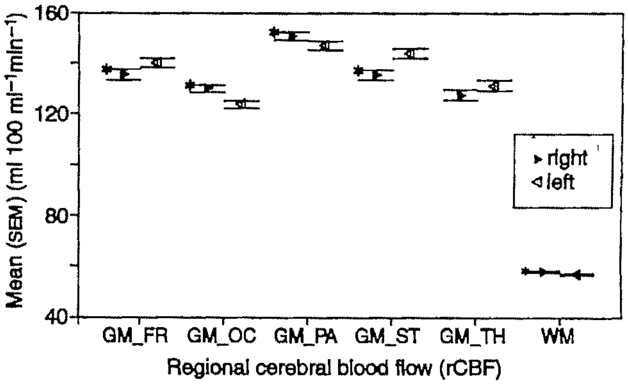

Fig 1 Interhemispheric differences in regional cerebral blood flow (GM_FR–grey matter, frontal; GM_OC–grey matter, occipital; GM_PA–grey matter, parietal; GM_ST–grey matter, striatal, GM_TH–grey matter, thalamic; WM–white matter). *Significance P<0.001. Values are given as mean (SEM).

Table 3 Values of drug effect on regional cerebral blood flow (rCBF, ml 100 ml^{-1} min^{-1}), regional cerebral blood volume (rCBV, ml 100 ml^{-1}), regional mean transit time (rMTT, s) and regional cerebrovascular resistance (rCVR, 10^4 N m^{-2} min 100 ml^{-1}), baseline *versus* remifentanil separated by hemispheres GM_FR–grey matter, frontal, GM_OC–grey matter, occipital, GM_PA–grey matter, parietal; GM_ST–grey matter, striatal, GM_TH–grey matter, thalamic, WM–white matter. *Significant to baseline P<0.001 Values are given as mean (SEM)

		Right hemisphere					**Left hemisphere**				
		Control		**Remifentanil**			**Control**		**Remifentanil**		
		Mean	SEM	**Mean**	SEM	***P*-value**	**Mean**	SEM	**Mean**	SEM	***P*-value**
GM_FR	rCBF	135.68	2.10	198.41	3.30	*	140.24	1.76	200.31	3.53	*
	rCBV	9.95	0.15	11.23	0.13	*	9.42	0.13	10.99	0.11	*
	rMTT	4.75	0.06	4.36	0.07	*	4.28	0.04	4.36	0.06	NS
	rCVR	1.18	0.02	0.96	0.02	*	1.10	0.01	0.99	0.02	*
GM_OC	rCBF	130.14	1.47	194.03	3.29	*	123.98	1.41	201.82	3.50	*
	rCBV	9.82	0.11	11.85	0.13	*	9.25	0.12	12.16	0.15	*
	rMTT	4.80	0.04	4.89	0.06	NS	4.75	0.05	4.76	0.06	NS
	rCVR	1.16	0.02	1.16	0.03	*	1.22	0.02	1.09	0.02	*
GM_PA	rCBF	150.97	1.67	214.50	3.17	*	147.23	1.82	193.22	3.03	*
	rCBV	10.70	0.14	12.91	0.15	*	9.64	0.11	12.02	0.13	*
	rMTT	4.45	0.04	4.66	0.06	*	4.37	0.04	4.76	0.05	*
	rCVR	1.03	0.01	0.97	0.02	*	1.11	0.01	1.02	0.02	*
GM_ST	rCBF	135.72	1.83	222.70	3.57	*	144.15	1.84	213.36	3.42	*
	rCBV	8.13	0.10	10.86	0.11	*	8.61	0.10	10.88	0.12	*
	rMTT	3.91	0.04	3.68	0.05	*	3.88	0.05	3.77	0.05	*
	rCVR	1.08	0.01	0.84	0.02		1.01	0.01	0.86	0.02	*
GM_TH	rCBF	127.70	2.07	197.70	5.97	*	133.95	2.01	186.46	5.08	*
	rCBV	9.00	0.16	9.98	0.17	*	9.98	0.21	10.28	0.17	*
	rMTT	4.49	0.06	4.32	0.06	*	4.69	0.08	4.45	0.09	*
	rCVR	1.14	0.02	1.09	0.03	*	1.08	0.02	1.09	0.03	*
WM	rCBF	58.02	0.37	79.44	0.83	*	57.08	0.39	77.53	0.69	*
	rCBV	5.03	0.05	5.59	0.03	*	4.87	0.04	5.82	0.04	*
	rMTT	5.50	0.05	5.32	0.04	*	5.44	0.04	5.48	0.05	NS
	rCVR	2.48	0.10	2.15	0.02	*	2.45	0.02	2.07	0.02	*

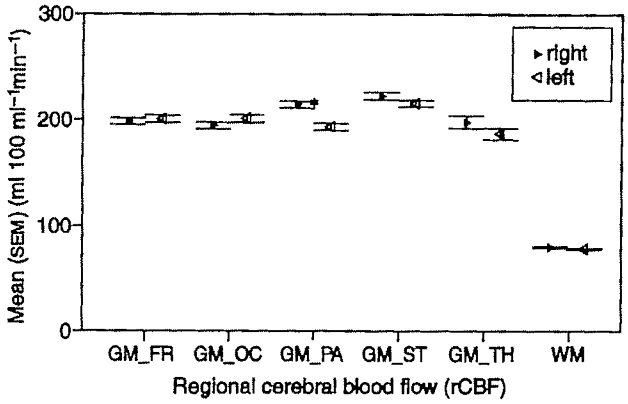

Fig 2 Interhemispheric differences in regional cerebral blood flow nearly eliminated by remifentanil (GM_FR–grey matter, frontal, GM_OC–grey matter, occipital; GM_PA–grey matter, parietal; GM_ST–grey matter, striatal; GM_TH–grey matter, thalamic, WM–white matter). *Significance *P*<0 001. Values are given as mean (SEM).

rCBV

In grey matter, rCBV ranged from 8.1 (SEM 0.5) to 10.7 (0.1) ml 100 ml^{-1}, whereas rCBV white matter was 5.0 (0.1) ml 100 ml^{-1} at baseline (Table 3). Remifentanil infusion increased rCBV in all regions studied. The increase was most pronounced in striatal, occipital and parietal rCBV, with the least change found in thalamic rCBV. Although the increase in white matter rCBV was slightly higher than in thalamic rCBV, white matter rCBV was at all times lower than grey matter rCBV, independent of both remifentanil and hemisphere. rCBV showed interhemispheric differences at baseline. Left-hemispheric rCBV was higher in striatal and thalamic grey matter but lower in parietal, frontal and occipital grey matter as compared with right-hemispheric rCBV. During remifentanil infusion, only left parietal rCBV remained lower than right-sided, but de novo left hemispheric white matter rCBV had become higher than right-hemispheric (Table 3).

rMTT

rMTT ranged from 3.80 (SEM 0.05) s to 4.80 (0.04) s in grey matter and was 5.50 (0.05) s in white matter at baseline (Table 3). Remifentanil diminished rMTT in most regions except occipital left frontal grey and left white matter. Interhemispheric rMTT differences in frontal grey matter were, in contrast to parietal grey matter, eliminated by remifentanil (Table 3).

rCVR

rCVR ranged from 1.03 (SEM 0.01) · to 2.48 (0.10) · 10^4 Nm^{-2} min at baseline (Table 3). Remifentanil diminished rCVR in all regions (Table 3).

Discussion

In the present volunteer study, remifentanil (0.1 μg kg^{-1} min^{-1}) increased rCBF and rCBV in grey and white matter regions. rMTT was decreased in most regions with the exception of occipital grey matter, whereas rCVR was decreased in all regions. Moreover, administration of remifentanil eliminated most of the interhemispheric differences present in rCBF, rCBV and rMTT at baseline.

The reported effects of opioids on human cerebral haemodynamics range from increase[21–23] to decrease[24–26] to no change at all.[17 27 28] Several theories on how opioids influence cerebral haemodynamics are currently discussed in the literature.

First, any increase in Pa_{CO_2} due to opioid-induced ventilatory depression should cause cerebral vasodilation, thereby leading to increases in CBF and CBV.[12] Cerebrovascular reactivity to CO_2 has been shown to remain intact during administration of remifentanil in humans.[29] In the present study, normocapnia was meticulously controlled by Et_{CO_2}, which correlates well with Pa_{CO_2}.[30–32] Therefore, it is unlikely that Pa_{CO_2}-induced cerebral vasodilation influenced rCBF or rCBV measurements during remifentanil infusion.

Second, opioids, especially when given as a bolus, may decrease MAP, which leads to autoregulatory cerebral vasodilation.[33 34] Using a continuous infusion of remifentanil in our volunteers, we observed a decrease in heart rate but not in MAP. Autoregulative vasodilation is therefore unlikely as the underlying mechanism for the observed increase in rCBF and rCBV, especially as autoregulation is not affected by remifentanil.[35]

In mammalian brain (e.g. rat, cat, human), although in lower density than in pain-processing areas, opioid receptors are present in the walls of cerebral vessels[36] and perivascular tissue.[9] Consequently, another theory speculates that opioids modulate cerebral haemodynamics through opioid receptor-mediated direct action on vascular smooth muscle cells.[36 37] In more recent studies, however, modulation of other vasoactive systems (e.g. NO,[38] prostanoids[39] or vasopressin[40]) by opioids as well as direct metabolic and excitatory effects[41–43] seem to be of greater significance.

In the present study, rCVR was calculated simply from the ratio of MAP to rCBF. This simplification is justified as each volunteer served as his own control and none of the volunteers showed clinical signs or MRI findings of intracranial pathology. The observed decrease in rCVR during remifentanil infusion prompted a corresponding increase in rCBV. The present data, however, did not permit discrimination between opioid receptor-mediated direct vasodilation and vasodilation by opioid modulation of other vasoactive systems.

rMTT defines the average time needed by a tracer to transit the region of interest.[20] In the present study, remifentanil increased rCBF and rCBV but decreased rMTT in all regions except occipital grey matter. As rMTT equals the ratio of rCBV to rCBF, the observed decrease in rMTT reflects a relatively greater increase in rCBF than in rCBV.

The most likely explanation for this extra increase in rCBF is increased demand, which can not be fully met by the simultaneously present vasodilation. It is entirely possible that this increased rCBF reflects a kind of imbalance in the inhibitory *vs* excitatory relationship of neuronal networks – so-called disinhibition – such as remifentanil in low doses decreases the activity of inhibitory but not excitatory input to neurons. Accordingly, the greatest tendency of both rCBF and rCBV to increase was seen in μ-opioid receptor-rich brain structures.

A different kind of imbalance between inhibitory and excitatory neuronal input is also described for the transition from the awake to the sleeping state when introducing inhalation anesthetics. For example, for sevoflurane, Olofsen and Dahan[44] demonstrated during this transition in consciousness, enhanced EEG activity, which can be designated 'cerebral excitement'. Accordingly, evidence of such cerebral excitement caused by opioids is given by several studies reporting increased cerebral metabolism and CBF in unanesthetized animals (e.g. rabbit[45] and monkey[46]).

If the observed sensation of warmth, feeling of comfort and the reported dreams of our volunteers were an expression of opioid-mediated cerebral excitement, this could explain why rCBF as well as rCBV also significantly increased in other brain regions less rich in opioid receptors Although metabolic parameters were not measured in the present study, it is entirely possible that, in awake individuals, cerebral excitement and/or disinhibition increase cerebral haemodynamics more than that by a purely vasomotoric effect of remifentanil. Causing disinhibition and excitement before depression seems to be a general characteristic of hypnotics and general anaesthetics.

In the case of opioids, a dependency on both dose and background medication for cerebral excitement and disinhibition most likely exists. Paris and colleagues[26] thus found an ~10–20 times higher dose of remifentanil had no influence on CBF velocity, and an ~50 times higher dose even diminished CBF velocity in anesthetized cardiac patients. In contrast, in healthy spontaneously breathing volunteers without background medication, Mayer and colleagues[28] found an ~50 times higher dose of sufentanil to have no influence on rCBF.

Therefore, opioid-related cerebral excitement and/or disinhibition causing increases in cerebral haemodynamics decrease as the dose of the opioid increases. This decrease in cerebral excitement and/or disinhibition is further accelerated by background medication. As soon as opioids alone or in combination with background medication enter the fields of metabolic depression, cerebral excitement and/or disinhibition no longer occur and cerebral haemodynamics consequently decreases.[47]

In a PET study, Perlmutter and colleagues[48] reported regional asymmetry of CBF, CBV and CMRO2 in right-handed normal subjects. Similarly, in our right-handed, normocapnic volunteers, interhemispheric differences in rCBF were found at baseline. Differences in study design (e.g. on-line controlled normocapnia in our study *vs* normocapnia controlled by intermittent blood–gas sampling[48]) might explain our different findings in interhemispheric rCBV. Technical differences originating from the use of PET[48] and MRI are a further explanation, as Ostergaard and colleagues[16] showed PET-CBV values to significantly differ from MRI-CBV values, which supports the hypothesized sensitivity of MRI to small vessels. The previously shown impact of the arterial input function on quantitative evaluation of contrast media-enhanced MRI perfusion measurements is further attributed to the differences between MRI and PET perfusion values.[49]

References

1 Lang E, Kapila A, Shlugman D, Hoke JF, Sebel PS, Glass PS. Reduction of isoflurane minimal alveolar concentration by remifentanil. *Anesthesiology* 1996, **85**: 721–8

2 Yarmush J, D'Angelo R, Kirkhart B, *et al.* A comparison of remifentanil and morphine sulfate for acute postoperative analgesia after total intravenous anesthesia with remifentanil and propofol *Anesthesiology* 1997; **87**. 235–43

3 James MK, Feldman PL, Schuster SV, Bilotta JM, Brackeen MF, Leighton HJ. Opioid receptor activity of GI 87084B, a novel ultra-short acting analgesic, in isolated tissues. *J Pharmacol Exp Ther* 1991, **259**: 712–8

4 Buerkle H, Dunbar S, Van Aken H. Remifentanil: a novel, short-acting, mu-opioid. *Anesth Analg* 1996; **83**: 646–51

5 Kubek MJ, Wilber JF. Regional distribution of leucine-enkephalin in hypothalamic and extrahypothalamic loci of the human nervous system. *Neurosci Lett* 1980; **18**: 155–61

6 Maurer R, Cortes R, Probst A, Palacios JM. Multiple opiate receptor in human brain: an autoradiographic investigation. *Life Sci* 1983; **33**· 231–4

7 Raynor K, Kong H, Mestek A, *et al.* Characterization of the cloned human mu opioid receptor. *J Pharmacol Exp Ther* 1995; **272**: 423–8

8 Cohen RM, Andreason PJ, Doudet DJ, Carson RE, Sunderland T. Opiate receptor avidity and cerebral blood flow in Alzheimer's disease. *J Neurol Sci* 1997; **148**. 171–80

9 Sandor P, De Jong W, De Wied D. Endorphinergic mechanisms in cerebral blood flow autoregulation. *Brain Res* 1986; **386**· 122–9

10 Armstead WM, Mirro R, Busija DW, Leffler CW. Opioids and the prostanoid system in the control of cerebral blood flow in hypotensive piglets. *J Cereb Blood Flow Metab* 1991; **11** 380–7

11 Dora E, Hines K, Kunos G, McLaughlin AC Significance of an opiate mechanism in the adjustment of cerebrocortical oxygen consumption and blood flow during hypercapnic stress. *Brain Res* 1992; **573**: 293–8

12 Benyo Z, Wahl M. Opiate receptor-mediated mechanisms in the regulation of cerebral blood flow. *Cerebrovasc Brain Metab Rev* 1996; **8**: 326–57

13 Wagner K, Detsch O, Kochs E, *et al* Regional cerebral blood flow in humans during remifentanil infusion. *Anesth Analg* 1999; **88**: S245

14 Muller-Gartner HW, Links JM, Prince JL, *et al.* Measurement of radiotracer concentration in brain grey matter using positron emission tomography: MRI-based correction for partial volume effects. *J Cereb Blood Flow Metab* 1992; **12**: 571–83

15 Aine CJ. A conceptual overview and critique of functional neuroimaging techniques in humans: I. MRI/FMRI and PET. *Crit Rev Neurobiol* 1995; **9**: 229–309

16 Ostergaard L, Smith DF, Vestergaard-Poulsen P, *et al.* Absolute cerebral blood flow and blood volume measured by magnetic resonance imaging bolus tracking: comparison with positron emission tomography values. *J Cereb Blood Flow Metab* 1998; **18**: 425–32

17 Moyer JH, Pontius R, Morris G, Hershberger R. Effect of morphine and n-allylnormorphine on cerebral haemodynamics and oxygen metabolism. *Circulation* 1957; **15**: 379–84

18 Minto CF, Schnider TW, Egan TD, *et al.* Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* 1997; **86**: 10–23

19 Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. *Anesthesiology* 1997; **86**: 24–33

20 Young WL, Ornstein E. Transit time. In: Cottrell JE, Smith DS, eds. *Anesthesia and Neurosurgery*. St Louis, MO: Mosby – Year Book, 1994; 58

21 Trindle MR, Dodson BA, Rampil IJ. Effects of fentanyl versus sufentanil in equianesthetic doses on middle cerebral artery blood flow velocity. *Anesthesiology* 1993; **78**: 454–60

22 Hanel F, Werner C, von Knobelsdorff G, Schulte am Esch J. The effects of fentanyl and sufentanil on cerebral hemodynamics. *J Neurosurg Anesthesiol* 1997; **9**: 223–7

23 Kolbitsch C, Hormann C, Schmidauer C, Ortler M, Burtscher J, Benzer A. Hypocapnia reverses the fentanyl-induced increase in cerebral blood flow velocity in awake humans. *J Neurosurg Anesthesiol* 1997; **9**: 313–5

24 Hoffman WE, Cunningham F, James MK, Baughman VL, Albrecht RF. Effects of remifentanil, a new short-acting opioid, on cerebral blood flow, brain electrical activity, and intracranial pressure in dogs anesthetized with isoflurane and nitrous oxide. *Anesthesiology* 1993; **79**: 107–13

25 Ostapkovich ND, Baker KZ, Fogarty-Mack P, Sisti MB, Young WL. Cerebral blood flow and CO_2 reactivity is similar during remifentanil/N_2O and fentanyl/N_2O anesthesia. *Anesthesiology* 1998; **89**: 358–63

26 Paris A, Scholz J, von Knobelsdorff G, Tonner PH, Schulte am Esch J. The effect of remifentanil on cerebral blood flow velocity. *Anesth Analg* 1998; **87**: 569–73

27 Jobes DR, Kennell EM, Bush GL, *et al.* Cerebral blood flow and metabolism during morphine-nitrous oxide anesthesia in man. *Anesthesiology* 1977; **47**: 16–8

28 Mayer N, Weinstabl C, Podreka I, Spiss CK. Sufentanil does not increase cerebral blood flow in healthy human volunteers. *Anesthesiology* 1990; **73**: 240–3

29 Baker KZ, Ostapkovich N, Sisti MB, Warner DS, Young WL. Intact cerebral blood flow reactivity during remifentanil/nitrous oxide anesthesia. *J Neurosurg Anesthesiol* 1997; **9**: 134–40

30 Bongard F, Wu Y, Lee T S, Klein S. Capnographic monitoring of extubated postoperative patients. *J Invest Surg* 1994; **7**: 259–64

31 Campbell FA, McLeod ME, Bissonnette B, Swartz JS. End-tidal carbon dioxide measurement in infants and children during and after general anaesthesia. *Can J Anaesth* 1994; **41**: 107–10

32 Young WL, Prohovnik I, Ornstein E, Ostapkovich N, Matteo RS. Cerebral blood flow reactivity to changes in carbon dioxide calculated using end-tidal versus arterial tensions. *J Cereb Blood Flow Metab* 1991; **11**: 1031–5

33 Schregel W, Weyerer W, Cunitz G. Opioids, cerebral circulation and intracranial pressure. *Anaesthesist* 1994; **43**: 421–30

34 Werner C. Effects of analgesia and sedation on cerebrovascular circulation, cerebral blood volume, cerebral metabolism and intracranial pressure. *Anaesthesist* 1995; **44**: 566–72

35 Warner DS, Hindman BJ, Todd MM, *et al.* Intracranial pressure and hemodynamic effects of remifentanil versus alfentanil in patients undergoing supratentorial craniotomy. *Anesth Analg* 1996; **83**: 348–53

36 Harder DR, Madden JA. Cellular mechanisms of opiate receptor stimulation in cat middle cerebral artery. *Eur J Pharmacol* 1984; **102**: 411–6

37 Waters A. Harder DR. Electromechanical coupling in rat basilar artery in response to morphine. *Neurosurgery* 1983; **13**: 676–80

38 Devine JO, Armstead WM. The role of nitric oxide in opioid-induced pial artery vasodilation. *Brain Res* 1995; **675**: 257–63

39 Armstead WM, Mirro R, Busija DW, Leffler CW. Prostanoids modulate opioid cerebrovascular responses in newborn pigs. *J Pharmacol Exp Ther* 1990; **255**: 1083–9

40 Armstead WM. Role of vasopressin in altered pial artery responses to dynorphin and beta-endorphin following brain injury. *J Neurotrauma* 1996; **13**: 115–23

41 Safo Y, Keykhah M, Smith DS, *et al.* High dose of narcotics and narcotic antagonists alter cerebral blood flow in the rat. *J Cereb Blood Flow Metab* 1983; **3**: 538–9

42 Safo Y, Young ML, Smith DS, *et al.* Effects of fentanyl on local cerebral blood flow in the rat. *Acta Anaesthesiol Scand* 1985, **29**: 594–8

43 Haffmans J, Heiligers J, Dzoljic MR, Saxena PR. Regional cerebral blood flow during enkephalin-induced seizures in the rat. *Neuropharmacology* 1986; **25**: 361–5

44 Olofsen E, Dahan A. The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequency of the electroencephalogram. *Anesthesiology* 1999; **90**: 1345–53

45 Koskinen LO, Bill A. Regional cerebral, ocular and peripheral vascular effects of naloxone and morphine in unanesthetized rabbits. *Acta Physiol Scand* 1983; **119**: 235–41

46 Miller RL, Forsyth RP, Melmon KL. Morphine-induced redistribution of cardiac output in the unanesthetized monkey. *Pharmacology* 1972; **7**: 138–48

47 Carlsson C, Smith DS, Keykhah MM, Englebach I, Harp JR. The effects of high-dose fentanyl on cerebral circulation and metabolism in rats. *Anesthesiology* 1982; **57**: 375–80

48 Perlmutter JS, Powers WJ, Herscovitch P, Fox PT, Raichle ME. Regional asymmetries of cerebral blood flow, blood volume, and oxygen utilization and extraction in normal subjects. *J Cereb Blood Flow Metab* 1987; **7**: 64–7

49 Ellinger R, Kremser Ch, Schocke M, Auer A, Felber S, Aicher F. The impact of the arterial input function (AIF) on quantitative evaluation of dynamic susceptibility contrast enhanced MR studies. In: *Proceedings ISMR*, 1998; 1207

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Enoximone pharmacokinetics in infants

P. D. Booker[1*], S. Gibbons[1], J. I. M. Stewart[2 3], A. Selby[2], E. Wilson-Smith[2] and M. Pozzi[2]

[1]*University of Liverpool, Liverpool,* [2]*Royal Liverpool Children's NHS Trust, Alder Hey, Eaton Road, Liverpool L12 2AP, UK.*
[3]*Present address: Queen's Medical Centre, Derby Road, Nottingham NG7 2UH, UK*
**Corresponding author*

Enoximone and enoximone sulphoxide concentrations were measured in plasma of 20 infants, median age 6.0 (range 0.6–49.7) weeks, during and after prolonged continuous infusions. Patients were given enoximone 1 mg kg^{-1} and an infusion at 10 μg kg^{-1} min^{-1} just before being weaned from cardiopulmonary bypass (CPB). The infusion was stopped when clinically indicated, after a median 97 (range 24–572) h. Arterial blood samples were taken 30 min and 12 h after CPB, every 24 h during the infusion, and then 2, 4, 8, 12 and 24 h after the infusion was stopped. Pharmacokinetic non-compartmental analysis was performed using TOPFIT software. Fourteen patients who retained normal hepatic function had a median (95% confidence intervals) clearance of 9.7 (6.3–14.1) ml min^{-1} kg^{-1}, elimination half-life of 5.2 (2.4–6.8) h and a volume of distribution of 3.6 (2.0–5.7) litre kg^{-1}. The six patients with significant hepatic dysfunction had a lower clearance, 5.7 (2.4–14.5) ml min^{-1} kg^{-1}, and significantly longer elimination half-life, 7.6 (6.5–10.9) h (P=0.02). Enoximone sulphoxide elimination half-life was significantly prolonged in three patients with renal dysfunction, 16.2 (10.5–17.7) h versus 6.9 (6.1–9.4) h (P=0.03). These results confirm that enoximone pharmacokinetics in infants is similar to that found in adults. The infusion rate of enoximone should be reduced if hepatic or renal dysfunction supervenes.

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Enoximone, a selective phosphodiesterase inhibitor, has significant inotropic and vasodilating properties that have proved useful in the postoperative management of infants and children having cardiac surgery.[1] The inotropic effects produced by enoximone are additive to β_1-adrenoreceptor agonists such as dobutamine[2] and epinephrine.[3 4] Enoximone does not require adrenergic receptors for its action so is particularly useful in patients with heart failure, who may have β_1-adrenoreceptor downregulation. One clinical study involving six adults in severe congestive heart failure who were given a single injection of enoximone, found a median steady-state volume of distribution of the parent drug of 4.2 (range 2.1–8.0) litres kg^{-1} and a median terminal elimination half-life of 6.2 (3.0–8.1) h.[5] Another study of adults in heart failure who received enoximone by infusion for 24 h, followed by a 12 h washout period, has demonstrated similar results.[6] There are no comparative data available for infants or children.

Enoximone is primarily metabolized in the liver by oxidation to enoximone sulphoxide. In a study of six adult patients with severe congestive heart failure, 74% of a single intravenous dose of enoximone was excreted in urine over the following 24 h as the sulphoxide metabolite, together with 0.5% of the parent drug.[5] The median terminal elimination half-life for the sulphoxide metabolite in these patients was 7.6 (range 6–11) h. Accurate in vivo determination of metabolite potency in humans is made somewhat problematic by the reversibility of enoximone metabolism, as reduction of enoximone sulphoxide to enoximone can occur both in kidney and liver. An experimental study in dogs suggests that the potency of the metabolite is about one-seventh that of the parent drug.[7]

For over 10 years, enoximone has been used as one of our first line inotropic drugs in infants and children recovering from cardiac surgery, though our dosage regimen has until now been based solely on paediatric clinical studies and published adult pharmacokinetic data. However, as no pharmacokinetic studies have been carried out in children, there remains some uncertainty as to the optimal loading dose and subsequent infusion rates of the drug. It is a tribute

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to the drug's wide therapeutic ratio that we continue to use it, despite knowing so little about its distribution and clearance in sick children. Nevertheless, there are potential dangers in giving too much enoximone: reported adverse effects include hyperosmolality[8] and hypotension.[9] One study of healthy adults demonstrated a significant correlation between the plasma concentration of both enoximone and its sulphoxide metabolite and effects on contractility.[10] Subsequent clinical studies have been unable to confirm this relationship in adults with cardiac failure[6] or in patients recovering from cardiac surgery,[11 12] though plasma concentrations between 1000 and 2000 ng ml^{-1} appear to be related with maximal clinical effects. One aim of our study was to discern whether we were achieving similar therapeutic plasma concentrations when using our standard dosage regimen. We also wished to determine whether enoximone pharmacokinetic values in infants were significantly different from those previously described in adults.

Methods

With local Ethics Committee approval and informed written parental consent, 20 infants who required inotropic support following cardiac surgery were studied. All infants had amethocaine gel applied to two small areas of skin 45 min preoperatively, but no other premedication was given. Anaesthesia was induced with thiopental 4 mg kg^{-1} and neuromuscular block produced with vecuronium 0.2 mg kg^{-1} h^{-1}. Alfentanil 10 μg kg^{-1} was given over 5 min before commencing an i.v. infusion at 2 μg kg^{-1} min^{-1}. Midazolam 0.2 mg kg^{-1} was injected into the bypass pump prime. Isoflurane (0.5%), in a mixture of air and oxygen, was given before and after cardiopulmonary bypass (CPB). Femoral arterial and central venous cannulae, a urinary catheter, temperature and oximeter probes were placed before surgery commenced.

A 1-ml arterial blood sample was taken during rewarming on CPB (zero control). Approximately 10 min before the anticipated discontinuation of CPB, a loading dose of enoximone 1 mg kg^{-1} was given over 2 min into a central vein. An infusion of enoximone 10 μg kg^{-1} min^{-1} was then started. A 1-ml blood sample was taken 30 min after successful weaning from CPB. Further samples were taken 12 and 24 h after CPB, and then every 24 h until the infusion was stopped. Clinical criteria determined when the enoximone infusion was discontinued. Another blood sample was taken immediately before stopping the infusion, and then at 2, 4, 8, 12 and 24 h. All blood samples were obtained from the arterial cannula, centrifuged, the serum separated and stored at −22°C until assay.

In addition to routine haemodynamic, haematological and biochemical monitoring, serum osmolality was measured each day in patients receiving infusions lasting > 48 h. This was compared to calculated values and the osmolal gap recorded. From the second postoperative day and thereafter, all patients had liver function tests measured daily for the duration of their enoximone infusion. Patients who had alanine aminotransferase and unconjugated bilirubin concentrations more than twice the normal values for >24 h were deemed to have significant hepatic dysfunction. Patients were deemed to have significant renal dysfunction if their serum creatinine concentration increased to more than twice the normal values for >24 h, and their urine output was <0.5 ml kg^{-1} h^{-1} for >6 h despite diuretic therapy and a normal blood pressure for their age.

The concentrations of enoximone and enoximone sulphoxide in the serum samples were determined using a high-performance liquid chromatographic (HPLC) technique, as described previously by Chan and co-workers.[13] The method involves addition of internal standard and organic solvent extraction, followed by separation with HPLC and detection by ultraviolet absorption. The assay range for both enoximone and enoximone sulphoxide was 50–3000 ng ml^{-1}. The coefficients of variation for enoximone at the level of the lowest and highest standards were 2.4% and 2.8%, respectively. The coefficients of variation for enoximone sulphoxide at the level of the lowest and highest standards were 0.4% and 2.4%, respectively. The lower limit of quantification (LLQ) for both enoximone and enoximone sulphoxide was 50 ng ml^{-1}.

Pharmacokinetic parameters for enoximone and enoximone sulphoxide were determined by non-compartmental analysis using TOPFIT computer software (Gustav Fischer Verlag, Stuttgart, Germany). The elimination rate constant (λ_z) was calculated by log linear regression of the terminal portion of the plasma drug concentration–time curve using the method of least squares. The terminal elimination half-life ($t_{\frac{1}{2}z}$) for enoximone and enoximone sulphoxide was calculated from ln $2/\lambda_z$ The area under the drug–time curve (from time=0 to infinity; AUC) was determined by the log-linear trapezoidal rule. Clearance (Cl) of enoximone was calculated from dose/AUC, where dose is the product of infusion rate, infusion duration and weight of individual. Calculation of the volume of distribution at steady-state required an accurate calculation of mean residence time. However, our data set was too complex to be analysed by normal non-compartmental analysis, and our calculations of mean residence time produced many obviously anomalous results. Hence, we have simply reported the volume of distribution during the elimination phase, calculated as the product of Cl and $1/\lambda_z$.

The Mann–Whitney test (SPSS for Windows, version 10.0) was used to compare pharmacokinetic parameters in patients with severe hepatic or renal dysfunction with those in patients with no evidence of organ dysfunction. Kendall's tau-*b* rank-order correlation coefficient was used to assess associations between age and calculated pharmacokinetic parameters. Partial correlations, controlling for hepatic dysfunction, were used to assess associations between duration of infusion or age and calculated pharmacokinetic parameters, and between age and peak concentration.

Table 1 Details of individual patients Organ 'dysfunction' signifies that biochemical markers of hepatic function were markedly deranged (H, hepatic) or that the patient was oliguric and serum creatinine was high (R, renal). TGA, transposition of the great arteries; TAPVC, total anomalous pulmonary venous connection; VSD, ventricular septal defect; ASD, atrial septal defect, HLHS, hypoplastic left heart syndrome, COR, cor triatriatum; FALLOT, tetralogy of Fallòt, PA, pulmonary atresia; MVD, mitral valve disease IQR, interquartile range

Patient	Age (weeks)	Weight (kg)	Duration of infusion (h)	Hepatic or renal dysfunction	Diagnosis
1	0.6	3.5	92	–	TGA
2	0.7	4.8	572	H + R	TAPVC
3	0.9	3.8	94	–	TGA
4	1.1	3.1	116	–	TGA
5	1.6	3.4	24	–	TGA
6	1.7	3.6	312	–	TGA, VSD
7	2.3	4.1	551	–	TGA
8	3.7	3.9	167	H	VSD, ASD
9	4.1	3.1	98	–	TGA
10	4.6	3.1	114	–	HLHS
11	7.4	3.9	94	–	COR, VSD
12	9.6	7.1	139	–	FALLOT
13	13.0	4.7	478	H + R	PA, VSD
14	16.7	5.4	28	–	ASD, VSD
15	17.1	5.2	24	–	VSD
16	17.4	3.4	124	H	VSD
17	23.4	5.3	71	H	FALLOT
18	34.7	5.2	96	–	FALLOT
19	35.7	7.2	93	–	FALLOT
20	49.7	5.6	46	H + R	MVD
Median	6.0	4.0	97		
IQR	15.7	1.9	83.8		
(range)	(0.6–49.7)	(3.1–7.2)	(24–572)		

Results

Individual patient details are given in Table 1. Six patients had significant hepatic dysfunction and three patients significant renal dysfunction during the course of the infusion. Although there was no significant correlation between age and any calculated pharmacokinetic parameters, we found a significant correlation between age and peak concentration, after controlling for hepatic dysfunction (P=0.03). There were no significant correlations between duration of infusion and any calculated pharmacokinetic parameters, when controlling for hepatic dysfunction. The plasma concentration of enoximone 30 min after discontinuation of CPB, peak concentration of enoximone, and calculated pharmacokinetic parameters for each patient are given in Table 2. At 30 min after discontinuation of CPB, plasma concentrations of enoximone ranged between 440 and 1316 ng ml^{-1}. Enoximone concentrations measured 12 h after CPB reached our target 'therapeutic' range (1000–2000 ng ml^{-1}) in 10/12 patients (samples were unobtainable at this time in eight patients due to logistical problems). In those 14 patients who retained normal hepatic function throughout the duration of their infusion, plasma concentrations of enoximone measured just before stopping the infusion were not significantly different to those measured after just 24 h of infusion, that is there was no evidence of drug accumulation. The median plasma concentrations (with 95% confidence intervals) of enoximone and enoximone sulphoxide measured at 24 h intervals during the infusions, for all patients, are given in Table 3.

Enoximone pharmacokinetics for those patients with organ dysfunction are compared to those who retained normal hepatic and renal function throughout their infusion in Table 4. There was no significant difference between the median volume of distribution during the elimination phase in patients with and without hepatic dysfunction. Although the median clearance in patients with hepatic dysfunction was lower than in those retaining normal hepatic function, this difference did not achieve statistical significance. Elimination half-life was significantly prolonged in patients with hepatic dysfunction compared to the other patients (P=0.02). The median peak enoximone concentration in the six patients with hepatic dysfunction (2974 ng ml^{-1}) was much higher than in the other patients (1483 ng ml^{-1}), though this did not achieve a statistically significant difference. Only patients with hepatic dysfunction had peak enoximone concentrations that exceeded 3000 ng ml^{-1}. An illustration of the marked difference between the enoximone concentrations measured in a patient with hepatic dysfunction, and one with normal hepatic function is given in Fig. 1. The median elimination half-life for enoximone sulphoxide in the three patients with renal dysfunction (16.2 h) was significantly longer than in the other patients (6.9 h, P=0.03).

The platelet count of all patients decreased after surgery, from a median value of 108 000 ml^{-1} 24 h post-CPB to a low of 73 000 ml^{-1} by day 4, but returning back spontaneously to >95 000 ml^{-1} by day 5 of the infusion. Measured serum osmolality exceeded 330 mOsm kg^{-1}, and the osmolal gap increased transiently to between 20 and 44 mOsm kg^{-1} in all

Table 2 Enoximone concentration 30 min after weaning from cardiopulmonary bypass (CPB), peak enoximone concentration, and calculated pharmacokinetic parameters for each individual patient NS, not sampled, IS, insufficient samples. IQR, interquartile range. 95% CI = 95% confidence intervals for the median

Patient	Enoximone conc. 30 min post-CPB (ng ml^{-1})	Enoximone peak conc. (ng ml^{-1})	Volume of distribution (Vd) (litre kg^{-1})	Clearance (Cl) (ml min^{-1} kg^{-1})	Elimination half-life ($t_{1/2}$) (h)	Enoximone sulphoxide elimination half-life (h)
1	695	2608	1.7	4 3	4 6	6.3
2	510	4375	4.0	4.2	10.9	17.7
3	NS	2760	3.1	6.3	5.6	7.1
4	440	801	2.0	16 2	1.4	2 9
5	529	708	15 5	18 9	9.4	6.7
6	884	2939	3 1	4.0	9 0	8.4
7	778	1468	5.4	9 2	6.8	8.0
8	718	6893	1 7	2.4	7 9	17 5
9	NS	1815	5 7	10.3	6 3	11 5
10	NS	1757	4 4	12 9	4.0	9.4
11	600	1213	4.1	9.6	4.9	7.4
12	632	960	8.3	14 1	6 8	11 7
13	1316	5272	1.8	2 9	7.3	10.5
14	496	1151	3.5	9.8	4 1	5.4
15	596	1089	2 1	10.4	2 4	5 0
16	NS	1211	10.6	14.5	8 5	6 4
17	782	1574	4.1	7 2	6.6	6 1
18	685	1498	3.6	7.7	5.5	6.6
19	710	1604	1 4	7 5	2.1	IS
20	470	1357	5 2	9.3	6.5	16.2
Median	658	1536	3 8	9.2	6.4	7.4
IQR	248	1556	3.3	7 5	3 5	5 2
95% CI	510–778	1211–2608	2.1–5 2	6.3–10 4	4.6–7.3	6.3–11 5

Table 3 Median (95% confidence intervals) plasma concentrations of enoximone and enoximone sulphoxide during constant rate infusion at 10 µg kg^{-1} min^{-1}. Duration of infusion was determined by clinical criteria alone. Sampling was not performed at all possible times in all patients for logistical reasons

Time (h) from starting infusion	Number of patients	Enoximone concentration (ng ml^{-1})	Enoximone sulphoxide concentration (ng ml^{-1})
12	12	990 (696–2065)	2812 (1840–5941)
24	16	1363 (960–2343)	2912 (2175–6523)
48	14	1349 (1039–2429)	3736 (2163–10 488)
72	12	1727 (1128–2760)	3662 (1826–8395)
96	10	1464 (581–3218)	3752 (935–8479)
120	6	2939 (592–3794)	7047 (1529–9774)
144	5	1627 (562–3194)	3768 (1405–9066)
168	5	2148 (677–5272)	2645 (1078–5081)

six patients with hepatic or renal dysfunction for up to 72 h. There were no other adverse effects that could reasonably be attributed to the enoximone therapy. All patients in the study made a full recovery from their surgery and were subsequently discharged from hospital.

Discussion

The median values calculated for enoximone clearance and elimination half-life in infants in this study were very similar to those previously found in adults. Although there are no directly comparable adult data, enoximone clearance in adults in chronic congestive cardiac failure ranged between 7 and 16 ml min^{-1} kg^{-1} and the elimination half-life between 4 and 7 h.[6 14] Although we were unable to calculate the volume of distribution at steady-state in our patients, our median value for volume of distribution during the elimination phase, 3.8 (95% CI 2.1–5.2) litres kg^{-1} is very similar to previously documented adult values (range 3.5–9.2 litres kg^{-1}).

This is the first study to examine enoximone pharmacokinetics in infants, and also the first to examine drug concentrations during and after prolonged infusions in any age group. Previous adult pharmacokinetic studies have been performed only after single intravenous injections or short infusions (<48 h).[6 10 11 15 16] In our study, the enoximone infusion was stopped when the patient's general condition, and ventricular function in particular, had improved sufficiently such that inotropic support was no longer required. If a patient required more than one inotropic drug, enoximone was always the last one to be discontinued. Inevitably, therefore, the patients receiving the most prolonged infusions of enoximone were, by definition, the patients who were sickest for the longest time period. However, there was no significant correlation between duration of infusion and calculated pharmacokinetic parameters. Nevertheless, we observed very high

Table 4 Median (95% confidence intervals) values of calculated pharmacokinetic parameters and peak enoximone concentration in patients with and without hepatic and renal dysfunction. Hepatic dysfunction was deemed to have occurred when concentrations of both alanine aminotransferase and unconjugated bilirubin were more than twice normal values for >24 h. Renal dysfunction was defined as a rising serum creatinine concentration >100 µmol litre^{-1} for >24 h, together with a urine output of <0.5 ml kg^{-1} h^{-1} for >6 h despite diuretic therapy and a normal arterial pressure. We were unable to obtain sufficient samples in one patient to perform the ES $t_{1/2}$ calculation. Vd, volume of distribution; Cl, clearance; EN $t_{1/2}$, elimination half-life of enoximone, ES $t_{1/2}$, elimination half-life of enoximone sulphoxide. *Significant difference between groups ($P<0.05$)

	Patients with normal hepatic function (n=14)	**Patients with hepatic dysfunction (n=6)**	**Patients with normal renal function (n=16)**	**Patients with renal dysfunction (n=3)**
Vd (litre kg^{-1})	3.6 (2.0–5.7)	4.1 (1.7–10.6)	–	—
Cl (ml min^{-1} kg^{-1})	9.7 (6.3–14.1)	5.7 (2.4–14.5)	–	—
EN $t_{1/2}$ (h)	5.2 (2.4–6.8)	7.6* (6.5–10.9)	–	—
Peak conc. (ng ml^{-1})	1483 (960–2608)	2974 (1212–6893)	–	—
ES $t_{1/2}$ (h)	–	–	6.9 (6.1–9.4)	16.2* (10.5–17.7)

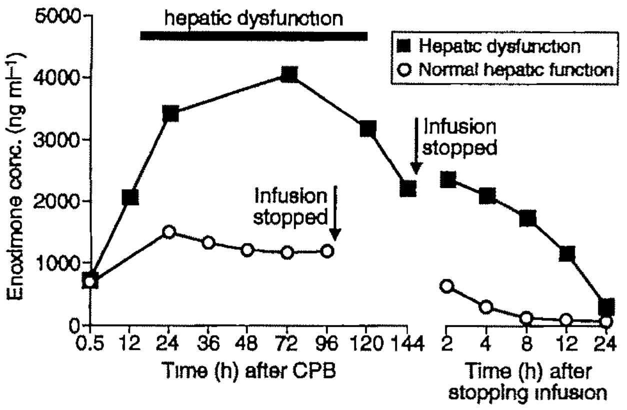

Fig 1 Plasma concentrations of enoximone in two infants receiving a constant infusion of enoximone 10 µg kg^{-1} min^{-1} after cardiac surgery. One patient (squares) had severe hepatic dysfunction for 3 days after surgery, causing a temporary increase in plasma enoximone concentration. These very high concentrations are in contrast to those measured in the other patient (circles) who retained normal hepatic function throughout.

plasma drug and metabolite concentrations in some sick patients at various times during their infusion. However, by the time the infusion was stopped, drug concentration had usually returned to near target levels. We observed no significant increase in plasma concentration during infusions of 72–144 h duration in those infants retaining normal hepatic and renal function. This suggests that an enoximone infusion rate of 10 µg kg^{-1} min^{-1} does not usually result in drug accumulation in neonates or infants who have normal hepatic function.

All patients who exhibited peak enoximone concentrations >3000 ng ml^{-1} demonstrated marked biochemical evidence of hepatic derangement. Clearance values of enoximone suggest that enoximone metabolism will be affected both by hepatic blood flow and by microsomal activity. A transient increase in drug plasma concentration during a constant rate infusion must reflect either a decrease in hepatic microsomal enzyme metabolic activity and/or a decrease in hepatic blood flow. The latter explanation seems more likely, as these perturbations usually occurred in the first 24–48 h after surgery, when cardiac output was particularly labile and vasoconstrictor inotropic drugs were also being used. Our criteria for a patient to be deemed as having hepatic dysfunction were relatively strict, though somewhat arbitrary: our measures of liver function had to rise to more than twice normal values for >24 h.[17] One clinical study in adults has demonstrated that low sulphoxidation activity does not correlate with the degree of hyperbilirubinaemia or histological severity of liver disease, and may even occur in otherwise normal individuals.[18] Nevertheless, the six patients who fulfilled our criteria for hepatic dysfunction had a reduced clearance rate and a significantly longer elimination half-life than the other 14 patients. As the neonate has reduced microsomal enzyme function compared to the older infant,[17] we were not surprised to find a significant correlation between age and peak concentration, after controlling for hepatic dysfunction (P=0.03). However, we were unable to demonstrate any significant correlation between age and any calculated pharmacokinetic parameter, after controlling for hepatic dysfunction.

The criteria we used to determine whether a patient should be deemed as having renal dysfunction were similar to those we normally use as indications for peritoneal dialysis, that is a rising creatinine >100 µmol litre^{-1} and a urine output <0.5 ml kg^{-1} h^{-1} for >6 h despite diuretic therapy and a normal arterial pressure. Only patients who had very poor renal function and required peritoneal dialysis demonstrated serum concentrations of enoximone sulphoxide >10 000 ng ml^{-1} at any time during their infusion. Prolonged elimination of the metabolite was demonstrated in all three patients with severe renal dysfunction.

There is one case report of an infant becoming hyperosmolar secondary to an enoximone infusion given at 20 µg kg^{-1} min^{-1} for several days.[8] This was thought to be due to propylene glycol accumulation, though the diluent also contains alcohol, which could have added to the problem. We both measured and calculated osmolality in all our patients who required prolonged infusions of enoximone, and found high transient osmolal gaps of 20–40 in six of our sickest patients, all of whom had hepatic dysfunction. No other patient exhibited an abnormal osmolal gap. Although this hyperosmolality may have been at least partially due to alcohol and propylene glycol, there were probably other contributing factors in these very sick infants. As vital organ function returned to normal, osmolal gaps similarly reduced to within normal limits, despite continuation of the same enoximone infusion rate.

In accordance with a previous adult study,[15] we could not demonstrate that enoximone produced clinically significant thrombocytopaenia. We believe that the post-CPB decrease in platelet count that we observed was similar to that often seen in sick patients not given enoximone, though a formal matched-pair comparison was not performed. Furthermore, although platelet counts decreased initially after CPB, they all returned spontaneously to normal values during the time course of the infusion.

We have confirmed that a loading dose of enoximone is necessary to achieve therapeutic concentrations in the early post-CPB period. The administration of the loading dose to the patient while still on CPB avoided any drug-induced hypotension. This study has demonstrated that enoximone 1 mg kg^{-1} given to the patient in the final few minutes of CPB will produce near therapeutic plasma concentrations in most patients by 30 min post-CPB, if an infusion at 10 $\mu g\ kg^{-1}\ min^{-1}$ is started at the same time. Adult data suggest that the optimum dosage regimen is one that achieves plasma concentrations ranging between 1000 and 2000 ng ml^{-1}, though this has not been confirmed for the paediatric age group. Although worthwhile therapeutic effects can be achieved at lower plasma concentrations than these, we aim for the maximum possible inotropic effect. This is because enoximone has a wide therapeutic ratio and substantially reduces the likelihood of having to use other potentially more noxious agents at high dose. Nevertheless, there is no therapeutic benefit in producing very high plasma concentrations, although enoximone appears devoid of obvious adverse effects during short-term infusions.

We conclude, therefore, that our current dosage regimen for enoximone, a 1 mg kg^{-1} loading dose followed by an infusion at 10 $\mu g\ kg^{-1}\ min^{-1}$, appears suitable for most patients. However, hepatic dysfunction may induce transient, very high concentrations in some individuals. Hence, we recommend that any clinical or biochemical indication of hepatic dysfunction should trigger a substantial reduction in the infusion rate. Similarly, isolated renal dysfunction resulting in oliguria should trigger a moderate reduction in the infusion rate.

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References

1 Innes PA, Frazer RS, Booker PD, *et al.* Comparison of the haemodynamic effects of dobutamine with enoximone after open heart surgery in small children. *Br J Anaesth* 1994; **72**: 77–81

2 Gilbert EM, Hershberger RE, Wiechmann RJ, Movsesian MA, Bristow MR. Pharmacologic and hemodynamic effects of combined beta-agonist stimulation and phosphodiesterase inhibition in the failing heart. *Chest* 1995; **108**: 1524–32

3 Boldt J, Kling D, Moosdorf R, Hempelmann G. Enoximone treatment of impaired myocardial function during cardiac surgery: combined effects with epinephrine. *J Cardiothorac Anesth* 1990; **4**: 462–8

4 Vincent JL, Leon M, Berre J, Melot C, Kahn RJ. Addition of enoximone to adrenergic agents in the management of severe heart failure. *Crit Care Med* 1992; **20**: 1102–6

5 Okerholm RA, Chan KY, Lang JF, Thompson GA, Ruberg SJ. Biotransformation and pharmacokinetic overview of enoximone and its sulfoxide metabolite. *Am J Cardiol* 1987; **60**: 21C–6C

6 Smith NA, Kates RE, Lebsack C, *et al.* Clinical pharmacology of intravenous enoximone: pharmacodynamics and pharmacokinetics in patients with heart failure. *Am Heart J* 1991; **122**: 755–63

7 Dage RC, Okerholm RA. Pharmacology and pharmacokinetics of enoximone. *Cardiology* 1990; **77**: 2–13

8 Huggon I, James I, Macrae D. Hyperosmolality related to propylene glycol in an infant treated with enoximone infusion. *BMJ* 1990; **301**: 19–20

9 Patel A, Caldicott LD, Skoyles JR, Das P, Sherry KM. Comparison of the haemodynamic effects of enoximone and piroximone in patients after cardiac surgery. *Br J Anaesth* 1993; **71**: 869–72

10 Belz GG, Meinicke T, Schafer-Korting M. The relationship between pharmacokinetics and pharmacodynamics of enoximone in healthy man. *Eur J Clin Pharmacol* 1988; **35**: 631–5

11 Desanger JP, Installe E, Harvengt C. Plasma enoximone concentrations in cardiac patients. *Curr Ther Res* 1990; **47**: 743–52

12 Gonzalez M, Desager J-P, Jaquemart J-L, Chenu P, Muller T, Installe E. Efficacy of enoximone in the management of refractory low-output states following cardiac surgery. *J Cardiothorac Vasc Anesth* 1988; **2**: 409–18

13 Chan KY, Ohlweiler DF, Lang JF, Okerholm RA. Simultaneous analysis of a new cardiotonic agent, MDL 17043, and its major metabolite in plasma by high-performance liquid chromatography. *J Chromat* 1984; **306**: 249–56

14 Jahnchen E, Trenk D. Pharmacology and pharmacokinetics of enoximone. *Z Kardiol* 1991; **80**: 21–6

15 Boldt J, Kling D, Dieterich HA, Marck P, Hempelmann G. The new phosphodiesterase inhibitor enoximone in patients following cardiac surgery – pharmacokinetics and influence on parameters of coagulation. *Intensive Care Med* 1990; **16**: 54–9

16 Morita S, Sawai Y, Heeg JF, Koike Y. Pharmacokinetics of enoximone after various intravenous administrations to healthy volunteers. *J Pharm Sci* 1995; **84**: 152–7

17 Rosenthal P. Assessing liver function and hyperbilirubinaemia in the newborn. National Academy of Clinical Biochemistry. *Clin Chem* 1997; **43**: 228–34

18 Olomu AB, Vickers CR, Waring RH, *et al.* High incidence of poor sulfoxidation in patients with primary biliary cirrhosis. *New Engl J Med* 1988; **318**: 1089–92

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Influence of tramadol on the ventilatory response to hypoxia in humans

P. M. Warren[1]*, J. H. Taylor[2], K. E. Nicholson[2], P. K. Wraith[3] and G. B. Drummond[4]

[1]Respiratory Medicine Unit, Department of Medical and Radiological Science, University of Edinburgh, Royal Infirmary, Edinburgh, [2]Department of Pharmacology, University of Edinburgh, [3]Department of Medical Physics, Western General Hospital, Edinburgh and [4]Department of Anaesthetics, University of Edinburgh, Royal Infirmary, Edinburgh, UK

**Corresponding author*

We studied the effect of tramadol on the ventilatory response to 7 min acute isocapnic hypoxia (Sp_{O_2} 85.1 (SD 0.4)%) during steady mild hypercapnia (PE'_{CO_2} 0.7 kPa above normoxic baseline) in 14 healthy volunteers (seven male). The acute hypoxic response was measured before and 1 h after oral placebo or tramadol (100 mg). After tramadol, ventilation during mild hypercapnia (mean 11.28 litres min^{-1}) was significantly less ($P<0.05$) than during placebo baseline (13.93 litres min^{-1}), tramadol baseline (14.63 litres min^{-1}), or after placebo (14.95 litres min^{-1}), confirming that tramadol has a small depressive effect on the hypercapnic ventilatory response. There was no significant difference in the hypoxic ventilation/Sp_{O_2} response (l min^{-1} %$^{-1}$) measured during the placebo baseline (0.99), placebo (1.18), tramadol baseline (0.78) or tramadol (0.68) runs. These data suggest that tramadol does not depress the hypoxic ventilatory response.

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Tramadol hydrochloride, licensed in the UK in 1994, is used for moderate acute and chronic pain. Although developed as a synthetic opioid, it has weak opioid receptor affinity[1] with only ~30% of its antinociceptor and analgesic actions antagonized by naloxone.[2] Much of its action is due to inhibition of the reuptake of the monoamines serotonin and noradrenaline at synapses in the descending neural pathways involved in analgesia.[1] Unlike other opioids, tramadol appears to be relatively free of the unwanted side effect of ventilatory depression causing only 10–15% reductions in normoxic ventilation and the hypercapnic ventilatory response[3 4] compared with the 30–50% decreases which occur following a dose of morphine or pethidine of similar potency.[3 5–7] However, the effect on the hypoxic ventilatory response is not known.

We have therefore studied the effect of oral tramadol on the ventilatory response to acute isocapnic hypoxia in normal subjects. The hypoxic ventilatory response was measured on a background of mild hypercapnia to mimic the postoperative situation.[8] In addition, we studied both men and women as sex-related differences have been found in the effect of morphine on ventilatory control in humans.[6]

Subjects and methods

Twenty healthy volunteers (nine males) gave written informed consent to participate in the study. None had a history of cardiorespiratory disease, or was receiving medication other than oral contraception at the time of study. The study was approved by the local Ethics Committees.

Each subject attended the laboratory on three occasions. The first visit was for familiarization. A medical history was obtained and the FEV_1 and FVC measured to confirm normal lung function. Subjects were then allowed to become accustomed to breathing through the facemask under normoxic, hypercapnic and hypoxic conditions. The second and third visits were study days and subjects were requested to fast for 3 h and to refrain from taking substances known to affect ventilation (e.g. caffeine) for a minimum of 8 h prior to study. On each study day the ventilatory response to hypoxia was measured before and 1 h after taking either tramadol 100 mg (ZYDOL, Searle) or matched placebo tablets. Drug and placebo study days were in random order and neither the subject nor assessor of ventilatory variable was aware of the treatment given.

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Subjects sat and read during the 1-h period between studies. Experimental studies were scheduled for the same time of day in any individual subject to minimize the effects of diurnal variation on the hypoxic ventilatory response. Females were studied within the first 10 days of a normal menses to ensure that they were not pregnant and to avoid the effect of increasing levels of progesterone in the luteal phase of the menstrual cycle.

Subjects were studied in a semi-recumbent position in a well-lit room and listened to music via headphones. They were instructed to stay awake and were roused if they appeared to fall asleep. Subjects breathed through a facemask (Hans Rudolf, series 8930) which enclosed both nose and mouth, was sealed to the face with gel (Aqua Gel, Adams Healthcare, UK), and was connected to a low-resistance two-way valve. Inspiratory gas mixtures prepared from primary gases (oxygen, nitrogen, carbon dioxide) were delivered to the subject through a T-piece attached to the inspiratory port of the two-way valve.

Ventilatory variables were recorded using methods described previously.[9] Expiratory gas passed via a heated pneumotachograph (Fleisch No. 2) through mixing and drying chambers to a Parkinson Cowan CD4 dry gas meter modified to give a digital signal. The integrated expiratory flow signal, which gave breath-by-breath tidal volume, was calibrated against the output of the CD4 gas meter every 10 litres to correct the flow signal. A mass spectrometer (VG Spectralab M), calibrated with four gas mixtures of known oxygen, carbon dioxide, nitrogen and argon concentration, measured inspiratory and end-tidal oxygen ($P\text{E}'_{\text{O}_2}$; kPa) and carbon dioxide ($P\text{E}'_{\text{CO}_2}$; kPa) partial pressures at the lips. Pulse oximetry (Sp_{O_2}, %; Ohmeda Biox 3700, set to a fast averaging time of 2 s), and electrocardiogram (Hewlett-Packard 78351A) were measured continuously throughout the study.

Breath-by-breath values of inspiratory time (T_I, s), expiratory time (T_E, s), total breath time ($T_\text{TOT}=T_\text{I}+T_\text{E}$, s), ventilatory frequency (f=60/T_TOT, b.p.m.), tidal volume (V_T, litres BTPS), instantaneous minute ventilation ($V_\text{E}^\text{inst}=f \times V_\text{T}$, litres min^{-1} BTPS), mean inspiratory flow ($V_\text{T} : T_\text{I}$, litres s^{-1}), and inspired and end-tidal partial pressures were digitized using an Olivetti PCS 286 computer and stored on disk for off-line analysis.

Oxygen consumption (litres min^{-1} STPD) and carbon dioxide output (litres min^{-1} STPD) were measured from collections of mixed expired gas made over a 2-min period, and the gas exchange ratio calculated. Concentrations of oxygen and carbon dioxide were measured using a Servomex oxygen analyser (Servomex model 570A) calibrated with air and 100% nitrogen, and a Gould capnograph (Mark IV) calibrated with four gas mixtures of known carbon dioxide concentrations, respectively.

Composition of the inspired gas was controlled by three mass-flow controllers (Bronkhorst Hi-Tech Types F-202AC and F-201AC with Bronkhorst E7200-AAA power supply and control unit). These supplied accurately controlled flows in the range 0–10 litres s^{-1} for carbon dioxide, 0–50 litres s^{-1} for oxygen and 0–100 litres s^{-1} for nitrogen. The gas input pressure for each controller was maintained at 2 bar by means of precision pressure regulator (0–4 bar, RS components) attached to the inlet to each mass-flow controller. The output of the three controllers was passed through a mixing chamber before being presented to the subject. A computer (Elonex PT-5120/1) was interfaced with the mass-flow controllers via a digital-to-analogue converter (Amplicon PC24) and also with the data-acquisition computer. A custom-written program displayed graded flow scales representing the output of each of the mass-flow controllers and breath-by-breath values of end-tidal oxygen and end-tidal carbon dioxide on the Elonex PC monitor. Adjustment of the graded scales using the computer mouse altered the output of the mass-flow controllers so that the required gas mixture delivered to the subject could be adjusted to achieve rapid, accurate changes in end-tidal partial pressures.

Each hypoxic ventilatory response measurement lasted 37 min. Subjects initially breathed room air for 15 min and duplicate measurements of oxygen consumption and carbon dioxide output were made between 8 and 13 min. The subjects then breathed a 21% oxygen mixture produced from the mass-flow controller system for a further 5 min to obtain a steady baseline. Mild hypercapnia was then induced for 10 min by increasing inspired carbon dioxide so that end-tidal $P\text{CO}_2$ was raised by 0.7 kPa above the previous baseline level. Inspired oxygen concentration was then decreased so that Sp_{O_2} was reduced to 85% for 7 min. The end-tidal was maintained at 0.7 kPa above the initial baseline level throughout hypoxia.

Mean values for all the ventilatory variables were calculated for each of the last 3 min of the baseline normoxic period, each of the last 3 min of the hypercapnic period, and each minute during hypercapnic hypoxia. In addition, mean values were calculated during the following 3-min periods of each run: normoxia (3 min before the onset of hypercapnia); hypercapnia (3 min before the onset of hypoxia): hypercapnic hypoxia (the last 3 min of hypoxia). The hypoxic ventilatory response was calculated as the ratio of the changes in V_E^inst and Sp_{O_2} occurring between the periods of hypercapnia and hypercapnic hypoxia ($V_\text{E}^\text{inst}/Sp_{\text{O}_2}$; litres min^{-1} %$^{-1}$).

Group means and SD for imposed ventilatory variables and group means and 95% confidence limits (CL) for studied variables in the three measurement periods were calculated for each run. Student's *t*-test was used to compare anthropometric data in men and women, and a paired *t*-test for within-run comparison of end-tidal $P\text{CO}_2$ during hypercapnia and hypoxia. Comparisons between runs for the group as a whole were made by one-way analysis of variance with *post hoc* comparisons made using the least significant difference method. Comparisons between runs for males and females considered separately were made using Friedman's non-parametric analysis of variance.

Significance was set at $P<0.05$. Computations were made using SPSS version 9 for Windows.

Results

Of the 20 subjects recruited to the study, two subjects (one male) were withdrawn from the study after experiencing severe nausea after taking tramadol. Three female subjects were unable to return for day 3 of the study because of very irregular menstrual cycles. One further male subject completed the study but had a markedly irregular breathing pattern in the final limb. The ventilatory variables could not be analysed accurately and the data from this subject were therefore excluded from the final analysis. Anthropometric data on the 14 subjects included in the analysis are given in Table 1. The men were significantly taller and had a higher BSA than the women, but there were no significant differences in age, weight, or calculated drug dose in mg kg^{-1}.

The pattern of ventilatory response was similar in all four limbs of the study. Ventilation increased slightly during mild hypercapnia, with a further substantial increase and little secondary decline during the 7 min of hypoxia (Fig. 1). Within runs, end-tidal $P\text{CO}_2$ was controlled, on average, to within 0.02 kPa of the hypercapnic level during hypercapnic hypoxia. End-tidal $P\text{CO}_2$ did not differ significantly between the periods of hypercapnia and hypercapnic hypoxia except in the period after tramadol when end-tidal $P\text{CO}_2$ was slightly but significantly greater during hypercapnic hypoxia than hypercapnia alone (Table 2). The mean difference after tramadol was 0.04 and the maximum-recorded increase of 0.08 kPa is within the error of the measurement.

Table 1 Means and SD or range for the subject details and drug dosage *Significant difference ($P<0.05$) between males and females

	Males	Females
n	7	7
Age (yr)	20.6 (18–22)	21.3 (20–22)
Height (cm)	179 (10)	168 (5)*
Weight (kg)	73.7 (9.4)	65.0 (8.6)
BSA (m^2)	1.9 (0.2)	1.7 (0.1)*
Drug dose (mg kg^{-1})	1.4 (0.2)	1.6 (0.2)

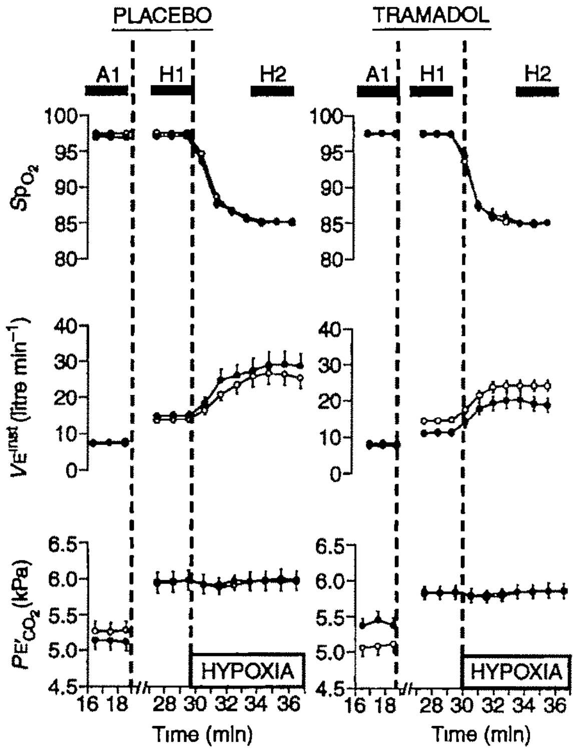

Fig 1 Oxygen saturation (Sp_{O_2}), instantaneous minute ventilation ($\dot{V}_E^{inst}$) and end-tidal $P\text{CO}_2$ (PE'_{CO_2}) plotted against time for both placebo (left-hand side) and tramadol (right-hand side) studies for baseline (open circles) and placebo or tramadol (closed circles). Mean values ± SD for each 1-min period are presented for the entire group. Mean values for each variable were calculated for the last 3 min of normoxia (A1), the last 3 min of hypercapnia (H1), and the last 3 min of hypercapnic hypoxia (H2) for each subject and used for comparison between runs

Table 2 Means (SD) for the imposed variables for the studied variables in the three measurement periods for baseline, placebo and tramadol runs *Significant difference between hypercapnic and hypercapnic hypoxia periods

		Normoxia	Hypercapnia	Hypercapnic hypoxia
End-tidal $P\text{CO}_2$ (kPa)				
	Baseline	5.27 (0.48)	5.97 (0.52)	5.99 (0.48)
	Placebo	5.14 (0.46)	5.96 (0.51)	5.97 (0.48)
	Baseline	5.08 (0.46)	5.83 (0.38)	5.86 (0.37)
	Tramadol	5.39 (0.34)	5.82 (0.39)	5.86 (0.39)*
End-tidal $P\text{CO}_2$ (kPa)				
	Baseline	12.87 (2.37)	13.02 (2.17)	6.15 (0.61)
	Placebo	13.72 (0.57)	13.84 (0.63)	6.16 (0.65)
	Baseline	13.77 (0.80)	13.85 (0.81)	6.11 (0.90)
	Tramadol	13.49 (0.75)	13.54 (0.69)	6.07 (0.98)
Sp_{O_2} (%)				
	Baseline	97.5 (0.7)	97.6 (0.7)	85.1 (0.3)
	Placebo	97.0 (0.7)	97.1 (0.5)	85.2 (0.3)
	Baseline	97.6 (0.7)	97.6 (0.6)	85.0 (0.5)
	Tramadol	97.5 (0.7)	97.4 (0.8)	85.1 (0.4)

Table 3 Mean (95% confidence limits) baseline metabolic values

	Oxygen consumption (litres min^{-1})	Carbon dioxide output (litres min^{-1})	Gas exchange ratio
Baseline	209 (183, 234)	163 (140, 186)	0.78 (0.74, 0.82)
Placebo	205 (184, 225)	162 (140, 183)	0.78 (0.74, 0.83)
Baseline	222 (190, 254)	179 (154, 204)	0.81 (0.78, 0.84)
Tramadol	202 (173, 232)	158 (132, 180)	0.78 (0.75, 0.81)

Table 4 Means (95% confidence limits) for the studied variables in the three measurement periods for baseline, placebo and tramadol runs *Indicates significant difference from placebo baseline, placebo and tramadol baseline values ($P<0.05$)

		Normoxia	Hypercapnia	Hypercapnic hypoxia
V_E^{inst} (litres min^{-1})				
	Baseline	7.39 (6.43, 8.33)	13.93 (11.94, 15.93)	26.14 (20.00, 32.27)
	Placebo	7.72 (6.41, 8.53)	14.95 (12.67, 17.23)	28.99 (21.14, 36.83)
	Baseline	8.21 (7.31, 9.11)	14.63 (13.02, 16.23)	24.45 (21.25, 27.65)
	Tramadol	7.54 (6.48, 8.6)	11.28* (9.27, 13.29)	19.64 (15.24, 24.04)
V_T (litre)				
	Baseline	0.50 (0.43, 0.56)	0.83 (0.72, 0.93)	1.31 (1.10, 1.52)
	Placebo	0.48 (0.42, 0.55)	0.85 (0.73, 0.97)	1.34 (1.10, 1.59)
	Baseline	0.52 (0.45, 0.58)	0.85 (0.73, 0.97)	1.31 (1.11, 1.50)
	Tramadol	0.45 (0.40, 0.49)	0.65* (0.56, 0.73)	1.02 (0.85, 1.19)
f (b.p.m.)				
	Baseline	15.3 (13.1, 17.5)	17.2 (15.7, 19.2)	20.2 (16.9, 23.4)
	Placebo	16.8 (14.2, 19.4)	18.1 (15.8, 20.4)	21.8 (17.1, 26.5)
	Baseline	16.7 (14.1, 19.3)	18.1 (15.6, 20.5)	19.7 (16.8, 22.5)
	Tramadol	17.2 (14.5, 20.0)	17.8 (14.9, 20.6)	19.7 (16.2, 23.1)

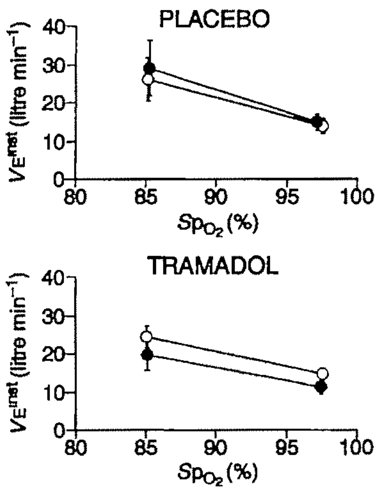

Fig 2 Plots of the V_E^{inst}/Sp_{O_2} relationship for the placebo (upper panel) and tramadol (lower panel) limbs of the study for the entire group Baseline studies are shown as open circles and studies after placebo or tramadol are shown as closed circles Data are given as mean values and confidence intervals

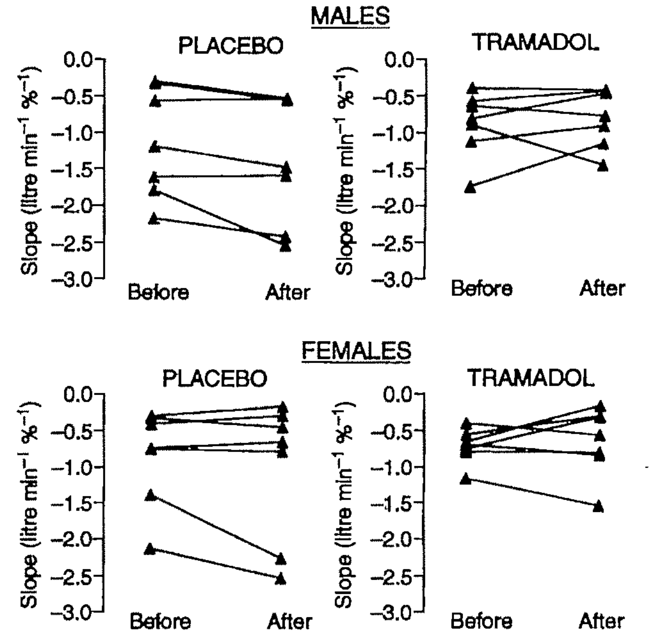

Fig 3 Plots of the individual V_E^{inst}/Sp_{O_2} relationships measured before and after either placebo or tramadol The data are grouped for males (upper panel) and females (lower panels). A lesser slope indicates a decreased hypoxic ventilatory drive

There were no significant differences in oxygen consumption, carbon dioxide output or the gas exchange ratio between the four runs (Table 3).

During normoxia there were no significant differences in the imposed variables between the four runs (Table 2), although end-tidal $P\text{CO}_2$ tended to be greater and end-tidal $P\text{CO}_2$ tended to be less after tramadol. Similarly, there were no significant differences between runs in the studied variables although V_E^{inst} and V_T tended to be less during the tramadol run (Table 4). During hypercapnia there were no significant differences between runs in the imposed variables (Table 2), but both V_T and V_E^{inst} during the tramadol run were significantly less than during either of the baseline runs or the placebo run (Table 4). During hypercapnic hypoxia there were no significant differences in either imposed or studied variables, although again V_E^{inst} tended to be less after tramadol.

There was no significant difference between the V_E^{inst}/Sp_{O_2} ratio for the placebo baseline (mean −0.99, CL −0.59, −1.40 litres min^{-1} $\%^{-1}$), placebo (mean −1.18, CL −0.66, −1.70 litres min^{-1} $\%^{-1}$), tramadol baseline (mean −0.78, CL −0.57, −0.98 litres min^{-1} $\%^{-1}$), and tramadol (mean −0.68, CL −0.43, −0.93 litres min^{-1} $\%^{-1}$) runs (Fig. 2). Similarly, there were no significant differences in the V_E^{inst}/Sp_{O_2} ratios between the four runs when men and women were considered separately (Fig. 3).

Discussion

We have shown that a standard analgesic dose of tramadol in normal subjects had no significant effect on the acute ventilatory response to isocapnic hypoxia. During mild hypercapnia, V_E^{inst} was significantly less after tramadol compared with either the baseline run or after placebo in spite of similar levels of end-tidal P_{CO_2}. This finding is consistent with a small effect of tramadol on the ventilatory response to hypercapnia.[4] Although tramadol did not have a significant effect on normoxic ventilation, the fact that V_E^{inst} and V_T tended to be ~10% less and end-tidal P_{CO_2} ~0.3 kPa greater after tramadol than during the tramadol baseline run is similar to changes reported previously in anaesthetized patients.[3 7]

Studies were performed on two separate days because the 5-h elimination half-life of tramadol[10] meant that the order of the placebo and active drug runs could not be randomized if the studies were performed on the same day. However, the hypoxic ventilatory response is known to vary substantially within and between days.[11] Individuals were studied at approximately the same time of day to minimize the effect of diurnal variation. To overcome the between-day variability, a baseline study was performed on each day and the effect of placebo or tramadol compared with the respective baseline measurements.

We were not able to measure serum tramadol concentrations to ensure that adequate concentrations had been achieved. A single oral dose of tramadol 100 mg given to fasting normal subjects is absorbed rapidly after an initial lag time of ~30 min, with serum concentrations reaching the analgesic threshold of 100 ng $litre^{-1}$ after ~40 min and reaching peak levels at 2 h.[10] However, there is considerable individual variability in bioavailability, with times for peak serum concentration varying between 1 and 4 h.[10] In this study, the repeated measurements were started 1 h after drug administration so that the repeated hypoxic challenge occurred after ~90 min when serum concentrations would be approaching maximum in most subjects. While this ensured that the hypoxic ventilatory response was unlikely to be depressed as a result of previous hypoxic exposure,[12] it is possible that peak serum concentrations had not been reached in some subjects. However, there was a reduction in hypercapnic V_E^{inst} of over 1.5 litres in nine out of 14 subjects after tramadol, whereas this only occurred in two subjects after placebo suggesting that active levels of tramadol had been achieved in most subjects. It is therefore unlikely that low drug concentrations account for the lack of depression of the hypoxic ventilatory response. Although 20 subjects were recruited, data were only obtained in 14 for a variety of reasons. Failure to detect a significant effect of tramadol on the hypoxic ventilatory response might therefore be a type 2 statistical error. However, this is unlikely to be the explanation as the study had a power of 0.9 to detect a change in the V_E^{inst}/Sp_{O_2} ratio of 0.5.

Dahan and colleagues[6] found a sex-dependent effect on the hypoxic ventilatory response which was independent of differences in weight, lean body mass, body surface area and calculated fat mass. In their study, morphine significantly reduced the initial ventilatory response to sustained hypoxia in women but not in men. We studied similar numbers of men and women. It was possible, therefore, that an effect in women was being masked by an absence of effect in the men. However, separate analysis of the results in seven men and eight women who completed the study showed no effect of tramadol on the initial hypoxic ventilatory response in either sex.

The *O*-desmethyltramadol metabolite of the (+) enantiomer of tramadol, produced by hepatic phase I metabolism by cytochrome P-450 2D6 (CYP2D6), has an affinity for the μ-opioid receptor which is ~200 times that of the parent compound.[13] It is likely, therefore, that the bulk of any ventilatory depression would be mediated by this metabolite. Approximately 10% of the Caucasian population are phenotypically poor metabolizers[14] and have a reduced analgesic effect of tramadol.[13] If, by chance, most of our subjects were poor metabolizers, then this could explain the absence of effect on the hypoxic ventilatory response. This effect could contribute to our findings but is unlikely to be the only explanation as tramadol suppressed the hypercapnic ventilatory response in nine out of 14 of our subjects.

The lack of suppression by tramadol of the hypoxic ventilatory response contrasts with the 50–60% suppression produced by morphine. Unlike morphine, tramadol produces its analgesic effects by a combination of low but preferential activity at μ-opioid receptors,[1] by inhibiting both noradrenaline and 5-hydroxytrypamine (5-HT) uptake,[1] and by facilitating 5-HT release.[15] The effects of these non-opioid actions of tramadol on ventilation are difficult to assess. A recent study showed that the 5-HT reuptake inhibitor fluoxetine caused a slight depression in resting ventilation in goats.[16] However, 5-HT can stimulate or depress ventilation depending on the subtype of receptor affected and the type of respiratory neurone activated.[17] Catecholamines have a similar dual effect on ventilation depending in part on whether the action is central or peripheral. Catecholamines administered to the respiratory neurones in the medulla usually cause depression,[18] whereas systemic administration stimulates breathing[19] and increases the ventilatory response to hypercapnia.[20] It is possible, therefore, that stimulation by 5-HT and noradrenaline offsets the opioid depressant effects of tramadol. The relative opioid receptor affinity of tramadol may also explain the ventilatory effects. In cats, depression of peripheral chemosensory discharge is mediated via δ receptors.[21] Tramadol has modest affinity for μ-receptors but extremely weak δ affinity. Tramadol may therefore suppress the ventilatory response to hypercapnia[4] via central μ-receptor activity leaving the peripheral component relatively intact. Studies with selective opioid receptor blockers would be required to confirm this.

In conclusion, we have shown that tramadol, in a standard clinical dose, does not significantly affect the ventilatory response to hypoxia. However, tramadol reduced resting tidal volume and insignificantly reduced ventilation, resembling the effects reported by Vickers and colleagues[3] at a dose of 1 mg kg^{-1}. Seitz and colleagues[4] also showed that tramadol caused a moderate depression of the hypercapnic ventilatory response. The significant reduction in hypercapnic ventilation after tramadol is in keeping with previous observations that tramadol causes a moderate depression of the hypercapnic ventilatory response,[4] and suggests that this suppression can be significant even at values which are only just above the normoxic resting level.

Acknowledgement

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References

1. Collart L, Luthy C, Dayer P. Partial inhibition of tramadol antinociceptive effect by naloxone in man. *Br J Clin Pharmac* 1993; **35**: 73P
2. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharm Exp Therap* 1992; **260**: 275–85
3. Vickers MD, O'Flaherty D, Szekely SM, Read M, Yoshizumi J. Tramadol: pain relief by an opioid without depression of respiration. *Anaesthesia* 1992; **47**: 291–6
4. Seitz W, Lubbe N, Fritz K, Sybrecht G, Kirchner E. Einfluß von Tramadol auf die ventilatorische CO_2-Antwort und den Mundokklusionsdruck. *Anaesthesist* 1985; **34**: 241–6
5. Weil JV, McCullough RE, Kline JS, Sodal IE. Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. *N Engl J Med* 1975; **292**: 1103–6
6. Dahan A, Sarton E, Teppema L, Olievier C. Sex-related differences in the influence of morphine on ventilatory control in humans. *Anesthesiology* 1998; **88**: 903–13
7. Tarkkila P, Tuominen M, Lindgren L. Comparison of respiratory effects of tramadol and pethidine. *Eur J Anaesth* 1998; **15**: 64–8
8. Jones JG, Sapsford DJ, Wheatley RG. Postoperative hypoxaemia: mechanisms and time course. *Anaesthesia* 1990; **45**: 566–73
9. Young CH, Drummond GB, Warren PM. Effect of a subanaesthetic concentration of halothane on the ventilatory response to sustained hypoxia in healthy humans. *Br J Anaesth* 1993; **71**: 642–7
10. Lintz W, Barth H, Osterloh G, Schmidt-Bothelt E. Bioavailability of enteral tramadol formulations. *Arzneim–Forsch/Drug Res* 1986; **36**: 1278–83
11. Sahn SA, Zwillich CW, Dick N, McCullough RE, Lakshminaryan S, Weil JW. Variability of ventilatory responses to hypoxia and hypercapnia. *J Appl Physiol* 1977; **43**: 1019–25
12. Easton PA, Slykerman LJ, Anthonisen NR. Recovery of the ventilatory response to hypoxia in normal adults. *J Appl Physiol* 1988; **64**: 521–8
13. Poulsen L, Arendt-Nielsen L, Brosen K, Sindrup SH. The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther* 1996; **60**: 636–44
14. Paar WD, Poche S, Gerloff J, Dengler HJ. Polymorphic CYP2D6 mediates O-demethylation of the opioid analgesic tramadol. *Eur J Clin Pharmacol* 1997; **53**: 235–9
15. Driessen B, Reimann W. Interaction of the central analgesic, tramadol, with the uptake and release of 5-hydroxytryptamine in the rat brain in vitro. *Br J Pharmacol* 1992; **105**: 147–51
16. Henderson DR, Konkle DM, Mitchell GS. Effects of serotonin reuptake inhibition on ventilatory control in goats. *Respir Physiol* 1999; **115**: 1–10
17. Bianchi AL, Denavit-Saubie M, Champagnat J. Central control of breathing in mammals: neuronal circuitry, membrane properties, and neurotransmitters. *Physiol Rev* 1995; **74**: 1–45
18. Champagnat J, Denavit-Saubie M, Henry JL, Leviel V. Catecholaminergic depressant effects on bulbar respiratory mechanisms. *Brain Res* 1979; **160**: 57–68
19. Lundholm L, Svedmyr N. Studies on the stimulating effects of adrenaline and noradrenaline on respiration in man. *Acta Physiol Scand* 1966; **67**: 65–75
20. Cunningham DJC, Hey EN, Lloyd BB. The effect of intravenous infusion of noradrenaline on the respiratory response to carbon dioxide in man. *Quart J Exp Physiol* 1958; **43**: 394–9
21. Kirby GC, McQueen DS. Characterization of opioid receptors in the cat carotid body involved in chemosensory depression in vivo. *Br J Pharmac* 1986; **88**: 889–98

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Use of intravenous patient-controlled analgesia for the documentation of synergy between tramadol and metamizol

A. Montes,[1] W. Warner[2] and M. M. Puig[1]*

[1]Anaesthesiology Research Unit, IMIM, Department of Anaesthesiology, Hospital Universitario del Mar, Paseo Maritimo 25, E-08003 Barcelona, Spain. [2]Department of Pharmacology, New York University College of Dentistry, New York, USA

**Corresponding author*

The quantification of the synergistic interactions (beneficial and adverse) of analgesic drug combinations in humans has been elusive. We propose a new procedure based on analgesic requirements (i.v.-PCA) and pain intensity (VAS-PI). One hundred and one post-hysterectomy patients received at the time of analgesia request (TAR) tramadol (100 mg, group I) or metamizol (1.2 g, group II) alone, or combined in 1:1 (III), 1:0.3 (IV) or 1:3 ratio (V). After 15 min, they received the same treatment by PCA. VAS-PI, analgesic consumption and adverse effects were assessed at TAR, and periodically for 24 h. Data were analysed using interaction indexes and isobolograms. All treatments produced equivalent VAS-PI, per cent efficacy and adverse effects. When drugs were combined in a 1:1 ratio, synergy was present for the analgesic and adverse effects; all other treatments were additive.

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Drug combinations are used widely in the treatment of acute and chronic pain, and constitute the basis for multimodal or balanced analgesia.[1 2] The rationale for the use of drug combinations is to obtain effective analgesia while decreasing the incidence and severity of side effects. When two or more drugs are administered simultaneously, their various pharmacological effects can be manifested independently and, in this instance, no interaction occurs (i.e. additive effects). However, observed effects may be different (of greater or lesser intensity) from those expected, and synergy or antagonism is said to occur. In order to establish a clinically relevant drug combination, the interaction of drugs with respect to both beneficial and adverse effects should be estimated.

One conventional means of evaluating drug interactions involves establishing the dose–response relationship of each drug individually and when combined in fixed dose ratios. From these experiments, isobolograms can be constructed which compare the doses of the drugs individually and in combination. The isobologram demonstrates the type of interaction in a manner that allows statistical evaluation.[3] Unfortunately, this experimental strategy is difficult to perform in humans, especially when evaluating analgesic drugs. In such studies, technical and ethical considerations make it difficult to establish reproducible dose–response relationships.[4]

In the present investigation, we evaluated drug interaction based on analgesic requirements determined by i.v. patient-controlled analgesia (PCA).[5 6] Our working hypothesis was that patients would self-administer or 'titrate' the analgesics to a consistent and satisfactory level of effect, regardless of the drug or drug combination used. Thus, the main purpose of our study was to evaluate a new protocol for the assessment and quantification of analgesic drug interactions in humans. A secondary goal was to investigate a possible interaction between tramadol and metamizol. These drugs were selected on the basis of their different mechanisms of action and similar duration.[7 8] Equianalgesic doses were used based on a potency ratio of 1:12.[6]

Methods

Experimental design

One hundred and one ASA I–II patients (age 18–70) scheduled for total abdominal hysterectomy (TAH) under general anaesthesia were included in the study. The protocol was approved by the Ethical Committee of our Institution, and all patients gave informed consent. Patients were visited

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the night before surgery and the use of PCA for postoperative pain relief was explained. Those who were unable to understand the PCA technique, those with morbid obesity and/or history of allergies to analgesic drugs were excluded from the study.

During the preoperative visit, patients were randomized using a numerical table into five groups of about 20 patients each (designated as groups I–V). The patients and investigators were unaware of the analgesic drug/s that would be used for each patient during the study.

All patients were premedicated with sublingual diazepam 10 mg administered 1 h before surgery. On arrival in the operating room, ECG, non-invasive arterial pressure, heart rate and Sp_{O_2} were monitored. An 18-gauge catheter was placed in the non-dominant hand and used for fluid administration intraoperatively, and for PCA in the postoperative period. A second 18-G catheter was placed in the other hand for the administration of anaesthetic drugs; this catheter was removed upon discharge from the recovery room.

Induction of anaesthesia was accomplished with fentanyl, midazolam, thiopental and atracurium. After tracheal intubation, mechanical ventilation was initiated and a 50% mixture of O_2/N_2O administered throughout surgery. Anaesthesia was maintained with a constant infusion of fentanyl 4 μg kg^{-1} h^{-1} and supplemental isoflurane in the concentrations required to maintain an adequate depth of anaesthesia (mean arterial pressure (MAP) and heart rate (HR) within 20% range of preoperative values). Inspired and expired isoflurane concentrations were monitored at 90–120-s intervals by mass spectrometry. Muscle relaxation was obtained with an infusion of atracurium and monitored with a nerve stimulator. The infusions of fentanyl and atracurium were ceased ~20–25 min before the end of surgery and residual muscle relaxation was reversed with neostigmine and atropine. All patients were extubated in the operating room.

Patients were transported to the recovery room where they were monitored in the standard manner. Time of first request for analgesia was noted (TAR), and the intensity of pain evaluated at rest, using a 0–10 visual analogue scale (VAS-PI).

At the TAR, a loading dose (10 ml) of one of the five analgesic treatments was administered i.v. The study groups and the corresponding drug mixtures included in the cassette or reservoir of the PCA pump are shown in Table 1. Thus, in group I, the PCA reservoir contained only tramadol at a concentration of 10 mg ml^{-1}; group II had only metamizol at a concentration of 120 mg ml^{-1}. The reservoir in group III contained a mixture of tramadol–metamizol combined at a 1:1 potency ratio (1:12 mg), that is tramadol 5 mg combined with metamizol 60 mg. Group IV received a combination of drugs at a ratio of 1:0.3 (i.e. 75:25); thus tramadol 7.5 mg plus metamizol 30 mg were combined. Group V received the same drugs combined at a 1:3 ratio (25:75), that is tramadol 2.5 mg plus metamizol 90 mg.

Fifteen minutes after the loading dose, VAS-PI was reassessed. At this time, PCA was initiated with the same analgesic ratio as the loading dose. The PCA administered boluses of 2 ml, with a lockout interval of 15 min and a maximal volume of 50 ml in 24 h. No baseline drug infusion was administered. The pumps (Pharmacia, Deltec 5800R) registered the number of boluses requested and the number delivered.

VAS-PI, pain relief and the doses of analgesics delivered were assessed at the following time-points after TAR: 15 min; and 1, 2, 4, 8, 12, 20 and 24 h. During the first hour, patients received a loading dose plus any drug self-administered by PCA during the following 45 min. Patients requesting additional analgesia at any time during the first 24 postoperative hours were rescued with i.v. morphine. In those patients, the PCA was discontinued and they were excluded from the study.

At each time of evaluation, patients were monitored for the occurrence of adverse effects: nausea, vomiting, sedation, pruritus, headache and pain on the site of injection. Sedation was evaluated using the Ramsey scale (graded 1–6)[9] and considered present when the value was ⩾3. Treatment for nausea and vomiting was i.v. metoclopramide, and for pruritus was diphenidramime.

Data analysis

Evaluation of the efficiency of the treatment (per cent pain relief) at the different time-points was performed according the following equation: VAS-PI at TAR (pain intensity before treatment) minus VAS-PI at a given time-point (pain intensity after treatment) divided by VAS-PI at the TAR (before treatment), multiplied by 100.

Table 1 Study groups Tramadol (TR) and metamizol (MTZ) were administered at fixed dose ratios based on a relative analgesic potency of 1·12 Actual doses administered were calculated by multiplying the total volume delivered by the concentration indicated in the table

Group	Ratio TR:MTZ	Concentration TR:MTZ (mg ml^{-1})	Number of patients/group
I	1:0	10 0	21
II	0:1	0·120	21
III	1:1	5·60	20
IV	1.0.3	7 5 30	19
V	1·3	2 5·90	20

Table 2 Patient characteristics and TAR. Results are mean values (SEM) (age, range)

Group	I (1:0)	II (0:1)	III (1:1)	IV (1:0.3)	V (1:3)
Age (yr)	44.8 (37–53)	46.9 (35–60)	48.5 (41–60)	46.9 (34–70)	47.4 (36–62)
Weight (kg)	66.7 (2.9)	64.5 (2.8)	68.7 (2.6)	66.0 (1.7)	69.2 (2.6)
Height (cm)	157 (0.9)	156 (1.5)	156 (1.6)	157 (1.2)	155 (1.4)
Duration of surgery (min)	107 (6)	97 (7)	103 (6)	103 (6)	111 (7)
TAR (min)	54.3 (8.6)	44.2 (7.2)	50.3 (6.8)	52.4 (6.0)	45.3 (5.9)

This calculation permits the distribution of patients into two groups: those that had an improvement of their pain equal or above 50%, and those that benefited to a lesser degree (<50% improvement). Thus, the efficacy of the treatment will be expressed as the number of patients in each group that experienced a 50% or greater pain relief.

Analysis of the interaction

The cumulative doses consumed at each time-point were used to calculate interaction indexes and for constructing isobols;[10] the calculation was possible because all drug combinations produced equivalent responses (VAS-PI) at each time of evaluation. For efficacy and adverse effects, dose–response relationships were obtained by plotting cumulative doses against efficacy and incidence of adverse effects, and the ED_{50} determined according to the method of Litchfield and Wilcoxon.[11] These values were then used to calculate interaction indexes. Interaction indexes (INT-I) permit a mathematical analysis of the nature of drug interactions and are obtained utilizing the following relationship:

$$d_a/D_a + d_b/D_B = 1$$

D_A and D_B are the doses of the drugs when used alone, while d_a and d_b are the doses of the same drugs when used in combination; in each case all producing the same response. Interaction indexes greater or lower than 1 demonstrate interactions that are less or more than additive, respectively. Statistical analysis (Student's *t*-test) of the interaction indexes was performed comparing the experimentally observed doses with those expected to occur had no interaction been present.[11]

Construction of isobols

Isobols are graphic representations of equally effective doses of two or more agents. The mean (SEM) doses of each drug that produces a given response are plotted on the axes of the graph. A zero interaction line (isobol) connects these isoeffective doses in the axis; lines connecting the upper and lower values of the SEM in the axis indicate the error of the isobol line. Doses of drug combinations producing the same effect are then plotted. Points falling on the diagonal line represent zero interaction (additivity), while those located above and below are antagonistic and synergistic, respectively. Mean and SEM were calculated for all the doses plotted, and points were considered to differ significantly if their SEMs did not overlap. In our study, isobols were constructed with doses of the drugs (individually and in combination) associated with the same pain intensity.

Statistical evaluation

Statistical calculations were performed as described by Tallarida and Murray.[11] Data are expressed as mean (SEM) or 95% confidence limits (CL). One-way analysis of variance (ANOVA) or chi-squared tests were used for comparison of the data.

Results

Patient characteristics, duration of surgery and TAR for each group are shown in Table 2. There were no significant differences.

Figure 1 illustrates mean pain intensity as a function of time for each of the five treatment groups. Pain intensity at the TAR (zero time-point) varied from 7.2 to 8.0. There were no significant differences (ANOVA). The decline in VAS-PI with time was found to be exponential with rate constants (*k*) that did not differ significantly between groups (*k* values ranging from –0.39 to –0.68).[11] All groups exhibited a rapid fall in VAS-PI over the first 2 h, and a slow decline thereafter. A test for parallelism[11] of the two segments of the graphs (represented by time-points 0–2 h and 4–24 h) demonstrated that, for each component, the slopes did not differ significantly between treatment groups (mean values 0.40 and 0.07, respectively). The similarity in the slopes of the lines representing the different treatments demonstrates that each provided a similar VAS-PI throughout the duration of the study.

The consistency of the VAS-PI at each time-point supports our assumption that patients would self-administer analgesics to a uniform end point. This similarity allows us to perform a null-point evaluation of the doses of the drugs and their interaction at the same VAS-PI. Thus, differences in the doses (not changes in response) of each drug individually or in combination will be the variable used to evaluate drug interactions.

The time to analgesia request (TAR) and the VAS-PI at that time did not differ significantly between the treatment groups. Fifteen minutes after the loading dose, VAS-PI was found to vary between 4.5 and 5.8 (Fig. 1). Analysis of

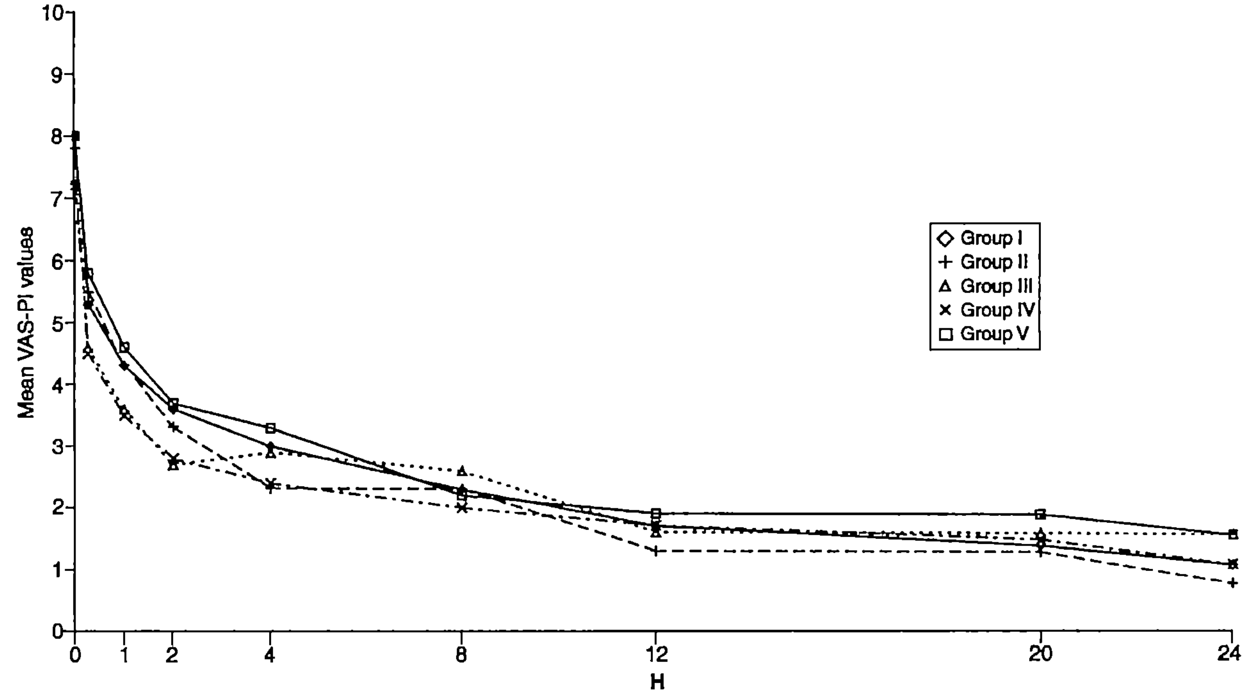

Fig 1 Mean VAS-PI values for each of the indicated times of evaluation. VAS-PI values obtained from each group were compared with the other treatments at every time-point (ANOVA). No significant differences were observed.

Table 3 Type of interaction of the combinations of tramadol and metamizol, and interaction indexes. The nature of the interaction was determined by the calculation of the interaction index (in brackets). Synergy occurs when the interaction index is significantly < 1 (Student's *t*-test; *$P<0.05$ and **$P<0.001$)

Time (h)	III (1:1)	IV (1:0.3)	V (1:3)
4	Synergy (0.79*)	Additive (0 94)	Additive (0.92)
8	Synergy (0.74**)	Additive (0.93)	Additive (0.97)
12	Synergy (0.71*)	Additive (0.88)	Additive (0.93)
20	Synergy (0.73**)	Additive (0 89)	Additive (0 97)
24	Synergy (0.73**)	Additive (0.93)	Additive (0.93)

variance of VAS-PI and of the per cent pain relief failed to reveal any significant differences. Mean per cent pain relief was 32.7% demonstrating that the loading doses produced similar but clinically insufficient pain relief. PCA was initiated 15 min after the loading dose, and VAS-PI assessed 1, 2, 4, 8, 12, 20 and 24 h afterwards. At each time-point, all treatments produced equivalent degrees of per cent pain relief. Pain relief increased over time, and starting at 2 h, all patients experienced at least 50% pain relief (54–88% range) for the duration of the study.

Efficacy was defined as the proportion of patients who experienced a 50% or greater degree of pain relief. In all treatment groups, efficacy was fully established by 2 h and continued throughout the study. Furthermore, there were no differences in efficacy between groups at any of the time-points (chi-squared test). A total of 14 patients were excluded from the study at 20 and 24 h. In three of these cases, patients required rescue analgesia after utilizing all the medication in the cassette; in 10 additional cases, patients elected not to continue with the study because of low pain intensity and the discomfort created by the i.v. line. For one patient, there was mechanical pump malfunction. All patient exclusions occurred after 20 and 24 h of treatment. The incidence of subject exclusion in the different groups did not differ significantly (chi-squared test).

At each time of evaluation, the cumulative volumes that were dispensed by the pump were recorded and converted into dose in mg. For groups III–V, the dose of each drug in the mixture was calculated (Table 1). The data were then analysed as cumulative dose and as milligrams per hour.

Analysis of drug interactions

The data show that all PCA treatments were equally effective in reducing pain. Drug interactions were evaluated using: (i) per cent pain relief at each time-point; and (ii) 50% efficacy. Because treatments produced equivalent effects, the results could be calculated arithmetically using interaction indexes, and graphically with isobolograms.

Per cent pain relief

Statistical evaluation of per cent pain relief revealed that when the drugs were used in a 1 : 1 combination (group III), a synergistic interaction occurred at 4 h and all subsequent time-points. The interaction indexes in this group varied from 0.79 to 0.71 ($P<0.05$ when compared with an index of 1). None of the other combinations (1:0.3 and 1:3, groups IV and V, respectively) were significantly different from additivity (Table 3).

Isobols were constructed showing the doses of drug combinations in groups III–V required to produce the same degree of analgesia (VAS-PI range 2.4–2.7) at the 8 h time-point. This time was selected as being representative of the time-points at which VAS-PI was most stable in the second segment of the curve (Fig. 1). The isobologram (Fig. 2) demonstrates synergy for the 1:1 combination, while no interaction was observed for the 1:0.3 and 1:3 drug ratios (additivity).

Efficacy of the treatments

The tramadol–metamizol interaction was also analysed utilizing cumulative doses of the drugs and the fraction of individuals with 50% pain relief (50% efficacy). From the quantal dose–response curves, we determined the doses at which half of the patients achieved this level of response (ED_{50}), and the values used to calculate the interaction indexes. The CL of the ED_{50} of each drug alone were compared with those of the drugs used in combination; if the 95% CL did not overlap the values were considered to be significantly different. The results (Table 4) also demonstrated statistically significant synergy in patients in group III (1:1 ratio) and no interaction with the other groups.

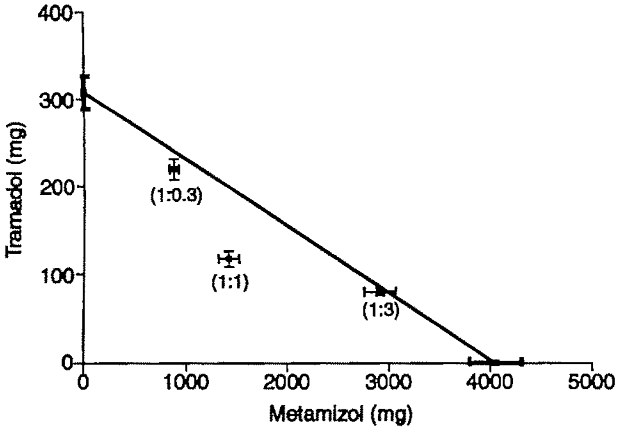

Fig 2 Isobolographic representation of the interaction of tramadol and metamizol at 8 h. The axes indicate the mean cumulative doses (SEM) of metamizol (abscissa) and tramadol (ordinate) that produce the same level of response (VAS-PI range 2.4–2.7). The diagonal line connects equally effective doses of each drug alone and designates additivity (zero interaction line) All other points in the graph were obtained by plotting each of the paired cumulative doses (SEM) in each treatment group The ratios of tramadol:metamizol are shown within brackets.

Adverse effects

At each time of evaluation patients were monitored for the occurrence of adverse effects: nausea, vomiting, sedation, pruritus, headache and pain on the site of injection. Nausea and vomiting were the most prevalent followed by sedation; the others were not analysed because they occurred infrequently.

We expressed these data quantally, and for each treatment group the results were analysed to determine: (i) the total number of adverse effects (global incidence) associated with each treatment; (ii) the number of patients with one or more adverse effects; and (iii) the time at which adverse effects occurred. The relatively low incidence of each one of the adverse effects precluded their separate or individual evaluation, and thus the results were analysed globally.

Forty-seven per cent of the patients reported one or more adverse effect (average 1–2) with a total of 71 events reported during the 24 h of observation. Neither the total number of adverse effects nor the number of patients experiencing them differed significantly between the treatment groups (chi-squared test). When adverse effects were present, they occurred most often at 4 and 8 h (27% each), and during the first hour (20%).

An analysis of the incidence of adverse effects indicated that the overall incidence of these events tended to decline as the concentration of metamizol in the mixture increased (correlation coefficient 0.64, $P<0.05$). The ED_{50} values for adverse events were obtained and used for the calculation of the interaction indexes (Table 4). Synergy was demonstrated in group III (1:1 mixture), while no significant interaction occurred in the other groups (additivity). The results demonstrate that when drugs are used in a 1:1 combination (group III) a synergistic interaction is present

Table 4 Type of interaction of the combinations of tramadol and metamizol, for efficacy and adverse effects at the ED_{50} values Mean ED_{50} values (95% CL) expressed in total mg were obtained from quantal dose–response curves in which efficacy and incidence of adverse effects are plotted against the cumulative doses. INT-I: interaction indexes. *$P<0.05$, NS (not significant when compared with additivity)

Group		III (1:1)	IV (1:0.3)	V (1:3)
Efficacy				
	ED_{50}	601 (448–807)	586 (478–719)	1417 (1121–1793)
	Interaction	Synergy	Additive	Additive
	INT-I	0.60*	1.10 (NS)	0.98 (NS)
Adverse effects				
	ED_{50}	1649 (1425–1905)	1355 (1103–1663)	5867 (4054–8489)
	Interaction	Synergy	Additive	Additive
	INT-I	0.62*	1.07 (NS)	1.3 (NS)

both for beneficial and undesirable effects; a comparison of the ED_{50} values reveals a therapeutic index of 2.7.

Discussion

The present study shows that the interaction between tramadol and metamizol is synergistic when the drugs are combined in a 1:1 potency ratio, and that both beneficial and adverse effects demonstrate the same type of interaction. We have utilized i.v. PCA as a means of evaluating the analgesic requirements needed to relieve postoperative pain. The drugs were selected because they are routinely used for the treatment of postoperative pain in our institution, their potency ratio is well established,[6] and they have a similar onset and duration of action.[7 8] Evaluation of drug interactions using PCA is not applicable to drugs with significantly different pharmacokinetic values.

PCA-based analgesic consumption is not a very precise method determining degree of analgesia,[12] but it is the only available method to determine objectively drug requirements. However, pain intensity was estimated by a VAS scale, a method which is widely accepted.[13]

The single use of the VAS-PI at rest for the evaluation of pain relief is a relative weakness of our study. In our original protocol, pain relief was also assessed by the nursing staff according to a four-point categorical scale. However, data collection was irregular and unreliable, thus precluding its use in the statistical evaluation. Similarly we were unable to use the number of boluses requested/delivered by the PCA pump each hour as a measure of the adequacy of the treatments. The data demonstrated considerable variability mainly in the number of requests per hour, while the number of boluses delivered/hour was more uniform; an analysis of variance failed to detect significant differences in either value.

The VAS-PI at the TAR was similar in all groups, and was used as the reference point for further calculations (per cent pain relief, per cent efficacy). Patients in each group titrated themselves to a comparable VAS-PI throughout the study, thus confirming our working hypotheses and validating the method of analysis. Our results are consistent with those previously reported that patients do not self-administer analgesics to a complete elimination of pain, but rather to a VAS-PI value <3,[14] a value that reflects a low to moderate pain intensity.[15]

In all patients, the loading doses by themselves failed to provide a satisfactory degree of analgesia (mean VAS-PI of 5.1). We think that this inadequacy was related to the high level of pain at the time of administration, a situation which would not occur in a clinical setting where analgesics are usually administered before experiencing severe pain. Consequently, in the present study, higher loading doses would have been appropriate.

During PCA, the VAS-PI declined rapidly, reaching a steady-state by about 2–4 h. When analysing the curves we were able to demonstrate that all treatment regimes followed a similar pattern of decline over time. The importance of these data is that, regardless of the regimen to which patients were assigned, all had a similar VAS-PI at each time of evaluation. This fact enabled the comparison of the doses of each drug (alone or in combination) needed to produce equivalent VAS-PIs. Figure 1 also shows that, at 1 and 2 h, patients were experiencing moderate pain (VAS-PI about 4) despite the possibility of self-administering additional medication, as at this time(s) the maximal doses allowed by the protocol were not exhausted. We are not able to explain this observation although the decrease in pain intensity (from severe to moderate) may have produced a subjective sensation of relief that made additional request(s) unnecessary.[16]

We defined efficacy as the proportion of patients who experienced a 50% or greater degree of pain relief, when compared with the VAS-PI at the TAR. However, because pain relief decreases gradually during the postoperative period, the calculated effect of the drugs includes the spontaneous decrease in pain intensity that is not drug related. Because VAS-PI at the TAR was unusually high (about 8), the calculated 50% efficacy does not necessarily reflect adequate analgesia, but the value was used as an additional method to assess and compare the effects. Regardless of the way in which the data were presented, all treatment regimens produced comparable results. The similarity of effects at each time-point permitted us to compare the doses of individual agents and their combination/s needed to produce equivalent results (i.e. VAS-PI, per cent relief, per cent efficacy).

Our data also show that per cent pain relief increased over time. Similarly, hourly drug usage also decreased up to 20 h. These data suggest a substantial decrease in pain intensity after 4 h, a fact that probably deserves further evaluation. The progressive decrease in VAS-PI (Fig. 1) together with the decline in the doses of the drugs self-administered shows that postoperative pain spontaneously diminished during the first 24 h. If pain remained constant, drug utilization would be expected to increase or remain high in order to reduce the VAS-PI to acceptable levels.

For the analysis of the interaction between tramadol and metamizol we used mathematical (combination indexes) and graphic (isobolograms) methods of evaluation. Both methods require that individual drugs and their combination produce the same level of response. When the drugs were used in a 1:1 ratio, synergy was demonstrated from 4 h onwards for the VAS-PI data. Similarly synergy was detected only in the same group for efficacy. Other treatment groups using 1:0.3 and 1:3 drug combinations were found to be additive. As with most other drug combinations, the mechanism/s involved in the change in the type of interaction when using different drug ratios are unknown. The evaluation of dose–response curves for adverse effects likewise demonstrated synergy when the drugs were used in a 1:1 combination. A comparison of the ED_{50} values (Table 4) for efficacy and adverse effects for the 1:1 combination reveals a therapeutic index of 2.7, indicating that the combination may be of therapeutic value. However, due to the number of patients and groups evaluated, and the incidence of adverse effects, these could only be evaluated globally and the results are not specific for nausea, vomiting or sedation. A larger number of patients using the same protocol would have to be evaluated in order to be able to demonstrate that each one of the adverse effects observed in the study is (or is not) dose dependent. Thus, the results show that when beneficial and pooled adverse effects were evaluated, tramadol and metamizol interact synergistically when combined in a 1:1 ratio.

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References

1 Kehlet H, Dahl JB. The value of 'multimodal' or 'balanced analgesia' in postoperative pain treatment. *Anesth Analg* 1993; **77**: 1048–56

2 Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997; **78**: 606–17

3 Puig MM, Pol O, Warner W. Interaction of morphine and clonidine on gastrointestinal transit in mice. *Anesthesiology* 1996; **85**: 1403–12

4 Eisenach JC, D'Angelo R, Taylor C, *et al.* An isobolographic study of epidural clonidine and fentanyl after cesarean section. *Anesthesiology* 1994; **79**: 285–90

5 McQuay HJ, Jadad AR, Carroll D, *et al.* Opioid sensitivity of chronic pain: a patient-controlled analgesia method. *Anaesthesia* 1992; **47**: 757–67

6 Lehmann KA. New developments in patient-controlled postoperative analgesia. *Ann Med* 1995; **27**: 271–82

7 Dayer P, Desmeules J, Collart L. *Pharmacology* of tramadol. *Drugs* 1997; **53**: 18–24

8 Levy M, Zylber-Katz E, Rosenkranz B. Clinical pharmacokinetics of dipyrone and its metabolites. *Clin Pharmacokinetics* 1995; **28**: 216–34

9 Hansen-Flaschen J, Cowen J, Polomano R. Beyond the Ramsey scale: need for a validated measure of sedating drug efficacy in the intensive care unit. *Crit Care Med* 1994; **22**: 732–3

10 Berenbaum MC. What is synergy? *Pharmacol Rev* 1989; **41**. 93–141

11 Tallarida RJ, Murray RB. *Manual of Pharmacologic Calculations with Computer Programs*. New York: Springer, 1986

12 Woodhouse A, Ward ME, Mather LE. Intra-subject variability in post-operative patient-controlled analgesia (PCA): is the patient equally satisfied with morphine, pethidine and fentanyl? *Pain* 1999; **80**: 545–51

13 Dexter F, Chesnut DH. Analysis of statistical test to compare visual analog scale measurements among groups. *Anesthesiology* 1995; **82**: 896–902

14 Liu S, Carpenter RL, Mulroy MF, *et al.* Intravenous versus epidural administration of hydromorphone. Effects on analgesia and recovery after radical retropubic prostatectomy. *Anesthesiology* 1995; **82**: 682–8

15 Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? *Pain* 1997; **72**: 95–7

16 Parker RK, Holtmann B, White PF. Effects of a night time opioid infusion with PCA therapy on patient comfort and analgesic requirements after abdominal hysterectomy. *Anesthesiology* 1992; **76**: 362–7

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Comparison of intravenous and oral ketoprofen for postoperative pain after adenoidectomy in children

H. Tuomilehto[1], H. Kokki[2]* and K. Tuovinen[3]

[1]*Department of Otorhinolaryngology,* [2]*Department of Anaesthesiology and Intensive Care, and* [3]*Department of Pharmacy, Kuopio University Hospital, PO Box 1777, FIN-70211 Kuopio, Finland*

**Corresponding author*

One hundred children, aged 1–9 yr, undergoing adenoidectomy were randomized to receive ketoprofen 1 mg kg^{-1} either i.v. with an oral placebo (*n*=40) or ketoprofen 1 mg kg^{-1} orally with an i.v. placebo (*n*=40), or both oral and i.v. placebo (*n*=20). The study design was prospective and double blind with parallel groups. The pain was assessed at rest and during swallowing using the Maunuksela pain scale (0=no pain, 10=worst possible pain) after surgery for 3 h. Fentanyl 0.5 μg kg^{-1} i.v. was given for rescue analgesia. Children in the i.v. group needed significantly less doses (1, 1–3; median and 10th/90th percentiles) of rescue analgesic compared with the oral group (2, 1–3; *P*=0.024). Of those who needed rescue analgesic, three out of 30 children in the i.v. group required three or more doses of fentanyl compared with 10 out of 28 children in the oral group. There were no differences between the groups with respect to pain scores, operation times, perioperative bleeding or frequency of adverse events.

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A low incidence of postoperative morbidity after day-case adenoidectomy in children is essential if we are to ensure parental and patient satisfaction.[1] Children who need more opioids in hospital, experience more intense pain at home during the first week after surgery,[2] and postoperative pain is related to behavioural problems.[3] Thus, effective pain treatment in children is essential.

Non-steroidal anti-inflammatory drugs (NSAIDs) are highly effective analgesics for treatment of mild to moderate pain.[1 4] In previous studies, we have shown the efficacy and safety of i.v. ketoprofen in small children following adenoidectomy.[5 6] Furthermore, the results show that i.v. ketoprofen, administered during the operation, was associated with not only analgesia but also reduced opioid consumption and adverse effects, such as vomiting.[7]

Administration by different routes of ketoprofen and other NSAIDs has not been compared properly.[8] If there is no difference in analgesic efficacy or adverse effects, the oral route is the most cost effective.

The aim of this study was to investigate whether the oral administration of ketoprofen is equivalent in analgesic efficacy to the i.v. route in the treatment of postoperative pain in small children following day-case adenoidectomy.

Patients and methods

This study was approved by our Ethics Committee, the National Agency for Medicines was notified of the use of ketoprofen in children <20 kg, and the study was conducted in accordance with the Declaration of Helsinki. Both parents and children of sufficient age received information regarding the study and written consent was obtained. We recruited 100 patients (1–9 yr, ASA 1 or 2) undergoing day-case adenoidectomy. Patients were excluded if they had known allergy to ketoprofen or other NSAIDs, asthma, haemorrhagic diathesis, kidney or liver dysfunction, or if they had any other contraindication for NSAIDs.

A randomized, prospective, double-blind, double-dummy, placebo-controlled, parallel groups study design was used. Children were allocated randomly to either one of two ketoprofen groups or a placebo group. The allocation was computer generated and a sealed envelope method was used to allow blinding. Forty children received ketoprofen orally, 40 children i.v., and 20 received placebo. In the oral group, children were given ketoprofen 1.0 mg kg^{-1} as a mixture (Orudis® 1 mg/ml mixture, Rhone-Poulenc Rorer, Cedex, France) 30 min before surgery, and placebo i.v. at induction (10 ml 0.9% normal saline) over 10 min. In the i.v.

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group, patients were given placebo mixture 30 min before surgery and ketoprofen 1.0 mg kg^{-1} in 10 ml 0.9% normal saline i.v. injected over 10 min at induction (Orudis® 50 mg/ml injection, Rhone-Poulenc Rorer, Helsinki, Finland). In the placebo group, children were given placebo mixture and normal saline injection. All study medications were prepared by a nurse not taking part in the study.

A standard anaesthetic technique was used. Each child was premedicated with diazepam 0.5 mg kg^{-1} orally (maximum of 10 mg) 30 min before induction. EMLA® cream (Astra, Södertälje, Sweden) was used at the venous puncture site. Atropine 0.01 mg kg^{-1} i.v. was given and anaesthesia induced with thiopental 5 mg kg^{-1} and fentanyl 1 µg kg^{-1} i.v. To facilitate tracheal intubation, cis-atracurium 0.1 mg kg^{-1} was given. Anaesthesia was maintained with 2–3% sevoflurane (inspired concentration) in 65% nitrous oxide in oxygen with intermittent positive pressure ventilation. On completion of the procedure, muscle relaxation was reversed with neostigmine 50 µg kg^{-1} and glycopyrrolate 10 µg kg^{-1}. All children received fentanyl 1 µg kg^{-1} at induction but no more opioids were allowed during the operation. For intraoperative fluid maintenance, all children were given 0.9% saline 5–10 ml kg^{-1} h^{-1}.

The adenoids were removed using a curettage technique. Haemostasis was controlled with temporary nasopharyngeal packs and electrocautery. Duration of surgery was recorded and at the end of the procedure the surgeon estimated the amount of bleeding using a five-point scale.[5] After the operation, children were transferred to the post-anaesthesia care unit (PACU) for continuous monitoring of vital signs and assessment of pain by specially trained nurses. Postoperative pain was assessed using the Maunuksela scale.[5 9] Pain expressed by the child at rest and during swallowing was assessed continuously and recorded every hour for up to 3 h. If the child was in pain with a pain score at rest of 3 or more, fentanyl 0.5 µg kg^{-1} i.v. was given. The dose was repeated at 5-min intervals until the pain had diminished to slight. No more than four doses were allowed in 1 h, and no other analgesic medication was permitted during the study. The last pain assessment and recording was made just before discharge, when the worst pain recorded during the PACU stay was noted. At discharge, sedation was assessed using a 100-mm visual analogue scale (VAS, 0='full alert' and 100='not arousable'). All adverse events were recorded.

Patients were discharged when they were awake, able to walk unaided, had stable vital signs for at least 1 h, had no or mild pain, had not vomited for 1 h, were able to tolerate clear fluids, had passed urine, and had no bleeding. All children received ketoprofen 1 mg kg^{-1} i.v. just before discharge.

The sample size was based on detecting a difference of 35% or more in the need for rescue analgesia between the i.v. and oral groups at a 0.05 significance level with 80% power. In addition, a small placebo group was included to avoid study bias based on our previous studies in pain treatment following adenoidectomy.[5 10] In a previous study, where a placebo group was not included, only 47% of the children who were given ketoprofen 2 mg kg^{-1} required rescue analgesia compared with 65% of the children in another previous study where children in the control group received placebo. This may be caused by observer bias, because it was known that in the study where placebo was not used, all the children had in fact received a previous analgesic. Therefore, a placebo group was included in this study and considered ethical.

Statistical analysis of continuous variables was performed using the Kruskal–Wallis test, and for *post hoc* analysis, the Mann–Whitney test with Bonferonni correction was used. For the categorical variables, the chi-squared test was used. $P<0.05$ was considered statistically significant. Results are presented as number of cases (%) or median (10th and 90th percentiles), as appropriate.

Results

There were no differences between study groups with respect to patient characteristics (Table 1). All except two children were ASA 1. There were no patient withdrawals from the study.

In the oral group, 28 out of 40 patients were given fentanyl for rescue analgesia, compared with 30 out of 40 patients in the i.v. group and 15 out of 20 patients in the placebo group.

Table 1 Patient characteristics Data are as number of cases or median with 10th/90th percentiles No significant differences

		Intravenous ketoprofen (*n*=40)	**Oral ketoprofen** (*n*=40)	**Placebo** (*n*=20)
Gender (male/female)		31/9	27/13	13/7
Weight (kg)	Median	14	17	17
	Percentiles	11–24	12–30	12–42
Height (cm)	Median	92	104	99
	Percentiles	81–124	83–127	78–144
Age (months)	Median	32	50	46
	Percentiles	16–82	20–101	15–101
ASA I/II		38/2	40/–	20/–

There was a significant difference between the study groups in number of fentanyl doses given (P=0.019). Children in the i.v. group needed significantly fewer doses compared with the oral group (P=0.024). There was no difference between the oral and placebo group. In the i.v. group, three out of 30 children needed three or more doses of fentanyl, compared with 10 out of 28 children in the oral group and six out of 15 children in the placebo group (P=0.032). The median time to the first fentanyl dose was 36 (7–67) min in the i.v. group, 23 (8–50) min in the oral group, and 23 (7–62) min in the placebo group.

There was no significant difference between groups with respect to Maunuksela pain scores (Table 2).

There was no difference with respect to duration of surgery (20 (10–35) min in the i.v. group, 21 (10–42) min in the oral group, and 17 (8–37) min in the placebo group). There was no difference in the extent of surgeon-assessed bleeding. There was no incidence of postoperative bleeding requiring re-operation, delay of discharge, admission to hospital or any other interventions.

On discharge, sedation scores were 7 (0–21) in the i.v. group, 6 (0–22) in the oral group, and 6 (0–19) in the placebo group.

Adverse events noted in the PACU are shown in Table 3. In the oral group, six out of 40 children had at least one adverse event, compared with eight out of 40 children in the i.v. group, and eight out of 20 children in the placebo group. Nausea, retching and vomiting were the most common adverse events with a similar incidence in the study groups. Two children in the oral group were admitted overnight because of protracted vomiting. One child in the placebo group was discharged later in the same afternoon because of delayed urination.

Discussion

In this study, ketoprofen 1 mg kg^{-1} given i.v. at the induction of anaesthesia provided better analgesic than a similar dose given orally 30 min before induction, as shown by reduced need for rescue analgesia in the i.v. group.

Table 2 Maunuksela pain scores Score 0 = 'no pain', 1–3 = 'slight pain', 4–6 = 'moderate pain', 7–9 = 'severe pain', 10 = 'worst possible pain'. Data are expressed as median with 10th/90th percentiles

	Intravenous ketoprofen (n=40)	**Oral ketoprofen (n=40)**	**Placebo (n=20)**
Pain at 1 h			
At rest	4	5	3
	0–8	0–8	0–9
During swallowing	5	6	6
	0–8	0–8	0–9
Pain at 2 h			
At rest	0	0	0
	0–5	0–4	0–8
During swallowing	0	0	0
	0–5	0–5	0–8
Worst pain in PACU			
At rest	4	5	3
	0–8	0–8	0–9
During swallowing	5	7	6
	0–8	0–8	0–9
Pain at discharge			
At rest	0	0	0
	0–1	0–2	0–2
During swallowing	0	0	0
	0–2	0–3	0–3

Table 3 Adverse events. Data are expressed as number of cases. No significant differences

	Intravenous ketoprofen (n=40)	**Oral ketoprofen (n=40)**	**Placebo (n=20)**
Nausea, retching, vomiting	5	5	4
Pain at the infusion site	2	1	2
Difficulty in urination	1	1	1
Shivering	–	1	–
Upper abdominal pain	–	1	–
Swelling in face and eyelids	–	–	1
Number of children with adverse events	8	6	8

Moreover, there was a tendency towards less requirement for rescue analgesia in the i.v. group compared to the oral group, although the difference was not significant. This was not expected, as ketoprofen syrup is absorbed rapidly (maximum plasma concentration occurs at 30 min, bioavailability >90%).[11]

The major mechanism of NSAID action is inhibition on prostaglandin synthesis,[12] hence the onset of the analgesia is delayed.[13] However, in addition to a peripheral action, i.v. ketoprofen also has a rapid central analgesic action.[14] To support this, Debruyne and co-workers have shown that administration of i.v. ketoprofen suppresses pain within 5–30 min.[15] Thus, we propose that the better analgesic action of the i.v. compared with the oral route in the present study is explained by a faster onset action.

Although the placebo group was included to avoid observational bias, it was interesting to notice that oral ketoprofen did not perform any better than placebo. This suggests that the dose used was inadequate or that drug absorption was incomplete or delayed, possibly relating to preoperative anxiety. On the other hand, this may also reflect delayed action of ketoprofen on prostaglandin synthesis. Kohler and co-workers showed a correlation between the analgesic effect of ketoprofen and drug plasma concentrations in adults. In their study, pain was at its lowest 2 h after oral administration of ketoprofen.[16] The use of a larger or earlier administration requires further study.

NSAIDs prolong bleeding time by inhibiting cyclooxygenase.[12] However, in the present study, no child receiving ketoprofen had postoperative bleeding requiring intervention or delayed discharge. In our earlier studies with ketoprofen, only one child out of 611 children experienced postoperative bleeding, but even he did not require further surgery.[2]

Pain assessment in small children is difficult because of their limited verbal abilities and understanding. Several other factors such as anxiety, excitement, fatigue and residual effects of anaesthetic agents can cause postoperative distress for children. This results in problems, not only for pain assessment, but also at home.[4 17] Consequently, for small children, pain scale assessments based on multiple variables are recommended. The Maunuksela pain scale, used in the present study, is a multidimensional assessment based on physiological, behavioural and contextual indicators. It has been validated for use in children from 1 to 18 yr.[9]

In contrast to our previous studies where we used isoflurane for maintenance, sevoflurane was used in the present study. Sevoflurane increases agitation during early recovery, probably due to postoperative pain.[18] Recently, Davis and co-workers have shown that intraoperatively administered NSAIDs reduced agitation in the immediate postoperative period.[19] In the present study, most of the children experienced moderate or severe pain during early recovery, so a proactive approach for pain management is recommended.[4 17]

References

1 Brennan LJ. Modern day-case anaesthesia for children. *Br J Anaesth* 1999; **83**: 91–103

2 Nikanne E, Kokki H, Tuovinen K. Postoperative pain after adenoidectomy in children. *Br J Anaesth* 1999; **82**: 886–9

3 Kotiniemi LH, Ryhanen PT, Moilanen IK. Behavioural changes in children following day-case surgery: a 4-week follow-up of 551 children. *Anaesthesia* 1997; **52**: 970–6

4 Wolf AR. Tears at bedtime: a pitfall of extending paediatric day-case surgery without extending analgesia. *Br J Anaesth* 1999; **82**: 319–20

5 Nikanne E, Kokki H, Tuovinen K. IV perioperative ketoprofen in small children during adenoidectomy. *Br J Anaesth* 1997; **78**. 24–7

6 Kokki H, Nikanne E, Tuovinen K. I.v. intraoperative ketoprofen in small children during adenoidectomy. a dose-finding study. *Br J Anaesth* 1998; **81**: 870–4

7 Kokki H, Homan E, Tuovinen K, Purhonen S. Preoperative treatment with i.v. ketoprofen reduces pain and vomiting in children after strabismus surgery. *Acta Anaesthesiol Scand* 1999; **43**: 13–8

8 Tramer MR, Williams JE, Carroll D, Wiffen PJ, Moore RA, McQuay H. Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review. *Acta Anaesthesiol Scand* 1998; **42**: 71–9

9 Maunuksela E-L, Olkkola KT, Korpela R. Measurement of pain in children with self-reporting and behavioral assessment *Clin Pharm Ther* 1987; **42**: 137–41

10 Nikanne E, Kokki H, Tuovinen K. Comparison of perioperative ketoprofen 2.0 mg kg^{-1} with 0.5 mg kg^{-1} i.v. in small children during adenoidectomy. *Br J Anaesth* 1997; **79**: 606–8

11 Kokki H, Jekunen A, Le Liboux A, Montay G, Heikkinen M. Pharmacokinetics of ketoprofen syrup in small children. *J Clin Pharmacol* 2000; **40**: 354–9

12 Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biol* 1971; **231**: 232–5

13 Maunuksela EL, Kokki H, Bullingham RES. Comparison of intravenous ketorolac with morphine for postoperative pain in children. *Clin Pharm Ther* 1992; **52**: 436–43

14 Willer JC, De Broucker T, Bussel B, Roby-Brami A, Harrewyn JM. Central analgesic effect of ketoprofen in humans: electrophysiological evidence for a supraspinal mechanism in a double-blind and cross-over study. *Pain* 1989; **38**: 1–7

15 Debruyne D, Hurault de Ligny B, Ryckelynck JP, Albessard F, Moulin M. Clinical pharmacokinetics of ketoprofen after single intravenous administration as a bolus or infusion. *Clin Pharmacokinet* 1987; **12**: 214–21

16 Kohler G, Primbs P, Morand J, Rubelt C. Correlation between ketoprofen plasma levels and analgesic effect in acute lumbar pain and radicular pain. *Clin Rheumatol* 1985; **4**: 399–404

17 Morton NS. Prevention and control of pain in children. *Br J Anaesth* 1999; **83**: 118–29

18 Lerman J, Davis PJ, Welborn LG, *et al.* Induction, recovery, and safety characteristics of sevoflurane in children undergoing ambulatory surgery. A comparison with halothane. *Anesthesiology* 1996; **84**: 1332–40

19 Davis P, Greenberg J, Gendelman M, Fertal K. Recovery characteristics of sevoflurane and halothane in preschool-aged children undergoing bilateral myringotomy and pressure equalization tube insertion. *Anesth Analg* 1999; **88**: 34–8

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Effect of peripheral morphine in a human model of acute inflammatory pain

J. Lillesø, N. A. Hammer, J. L. Pedersen and H. Kehlet*

Department of Surgical Gastroenterology, Hvidovre University Hospital, Kettegaard Allé 30, DK-2650 Hvidovre, Denmark

**Corresponding author*

Several studies have demonstrated the presence of opioid inducible receptors on peripheral nerves and peripheral antinociceptive effects of opioids. However, the effects of peripheral opioid administration in man are controversial. Our study used a randomized, double-blind, placebo-controlled, three-way crossover design in a human model of acute inflammatory pain (heat injury). We studied 18 healthy volunteers who each received morphine locally (2 mg), morphine systemically (2 mg), or placebo on three separate study days. The subjects received morphine infiltration subcutaneously (s.c.). 1 h before heat injury (47°C, 7 min) and naloxone infiltration s.c. (0.2 mg) 2.5 h after the heat injury. Hyperalgesia to mechanical and heat stimuli were examined using von Frey hairs and thermodes, and pain was rated using a visual analogue scale. The burns produced significant hyperalgesia, but local morphine infiltration neither reduced pain during the burn, nor primary or secondary hyperalgesia to mechanical and heat stimuli after the burn. In conclusion, peripherally applied morphine had no acute antinociceptive effects in this human model of acute inflammatory pain.

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The presence of opioid receptors has been demonstrated on peripheral terminals of thinly myelinated and unmyelinated nerves as well as on lymphocytes.[1–4] Inflammation may upregulate peripheral opioid receptors and the density appears to increase minutes to hours after an inflammatory reaction is initiated.[1 2] These findings suggest that opioids may have peripheral analgesic effects.

The analgesic effect of intra-articular opioid administration in the knee cavity has been studied extensively, and it has been concluded that intra-articular morphine may have some effect in reducing postoperative pain intensity, but final conclusions were hindered by flaws in designs and samples sizes of the studies.[5] Peripheral analgesic effects of opioids applied at extra-articular sites have been difficult to demonstrate, and a recent review concluded on the basis of 26 trials with data from 952 patients that there was no evidence for a clinically relevant peripheral analgesic effect of opioids in acute extra-articular pain.[6]

However, in the view of the clinical potential, there is a need for further human studies investigating the analgesic effects of peripheral morphine. The aim of our study was to examine the antinociceptive effect of morphine infiltrated subcutaneously (s.c.) in a human model of acute inflammatory pain. One trial has previously tested morphine in a similar burn model, but with limited sensory assessments and without systemic morphine as control.[7]

Methods

We studied 18 healthy volunteers (16 men) who were aged 22–48 yr. Informed consent was obtained from all subjects and the protocol was approved by the Municipal Ethical Committee of Copenhagen. During a pre-study training session, they were interviewed about their health history and were given a physical examination. In this session the volunteers experienced the burn and trained all assessments performed during the study.

The study used a randomized, double-blind, placebo-controlled, three-way crossover design. Each volunteer received either morphine (2 mg, 5 ml) s.c. in the burn injury area (local), morphine in the corresponding area on the opposite leg (systemic), or saline (0.9%, 5 ml) in both legs (placebo) on three study days separated by 2 weeks. When subjects received morphine, they received saline in the opposite leg. The order of the study days was randomized en bloc, so the treatments were equally distributed over the

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three study days. Morphine or placebo (saline) was injected after baseline measurements and measurements were repeated thereafter. The burn was induced on the non-dominant leg 1 h after the injections, and measurements were made at 0, 1 and 2 h after the burn. Subjects received naloxone (0.2 mg, 5 ml) in both areas, 2 h and 25 min after the burn injury, and measurements were repeated 30 and 90 min after the naloxone injections. The order and duration of the different measurements has been described previously.[8] All testing was performed by two experimenters in a quiet room at a temperature of 23–26°C. All subjects were tested by the same experimenter at the same time of the day on the three study days. The subjects were resting in a relaxed position and instructed to keep their eyes closed during all measurements.

All injections were given using a needle, 40 mm long with an external diameter of 0.4 mm. Morphine (SAD, Copenhagen, Denmark) was used at the concentration of 0.4 mg ml^{-1} (pH 4.1), naloxone (Du Pont Pharma, Meda AS, Copenhagen, Denmark) at the concentration of 0.04 mg ml^{-1} (pH 4.3). In all injections the volume was 5 ml. The injections were given from opposite corners of the 50×25-mm drawn rectangles, 2.5 ml from each corner, injected in a fan-like manner, in order to distribute the volume evenly in the rectangle. The injections were made in the most superficial part of the s.c. tissue. A person not involved in the testing administered the injections and prepared the morphine and placebo. Subjects were asked to evaluate the pain associated with each injection, using a visual analogue scale (VAS 0–100).

Burns were produced on the medial part of the non-dominant distal leg with a 50×25-mm thermode (Thermotest, Somedic A/B, Stockholm, Sweden).[8] The burns were induced in the same area on the three study days. The thermode (47 C) was applied to the skin for 7 min under standardized pressure (6.9 kPa). This caused redness without blistering.

The pain was rated with a VAS at the start and every minute during the burn injury. The scale was anchored by the descriptors, 'no pain' (0) and 'worst pain imaginable' (100). Verbal descriptors were added at 2 mm (weak pain), 8 mm (mild pain), 18 mm (moderate pain), 39 mm (intense pain) and 74 mm (very intense pain) to make the scale more comprehensible.[8] The subjects rated the pain with a slider on a plastic device that was pulled along a 10 cm line between the end points. The numeric value of the rating was read on the back of the device by the experimenter.

The mechanical pain threshold within the injury area was determined by pinprick with nine progressively rigid von Frey hairs (Senselab Aesthesiometer, Somedic A/B, Stockholm, Sweden) numbered one–nine (force of hairs: hair 1=6 mN, 2=9 mN, 3=17 mN, 4=27 mN, 5=46 mN, 6=77 mN, 7=118 mN, 8=228 mN, 9=314 mN). Suprathreshold pain responses to mechanical stimuli were assessed using the VAS following stimuli with a von Frey hair (314 mN). The area of mechanical hyperalgesia to punctate stimuli that developed around the burn area was assessed using a rigid von Frey hair (428 mN).[8]

Thermal thresholds were determined using a computerized contact thermode (Somedic A/B, Stockholm, Sweden).[8] All thresholds were assessed using a 25×50-mm thermode, and determined as the average of three trials performed at 9-s intervals, from a baseline temperature of 32°C, and with a rate of change of 1°C s^{-1}. The upper cut-off limit was 52°C. The pain response (VAS 0–100) to heat was evaluated with a heat stimulus (15×25-mm thermode) of 45°C lasting 5 s, preceded by a temperature rise from 40 to 45°C over 5 s.

The subjects completed a questionnaire at the end of each day concerning the presence (yes/no responses) of euphoria, nausea, bluntness, headache, dizziness, confusion, feeling drunk, itching and restlessness. When side effects were present, these were rated as weak, moderate or marked.

Normality of raw data and differences between groups were evaluated using the Shapiro–Wilk's W-test.[9] Data are presented as means or medians dependent on the distribution (normal or skewed), and comparisons were made using the Student's *t*-test for a paired design, when the differences showed normal distributions,[11] whereas differences showing non-normal distributions were analysed using the Wilcoxon matched-pairs test. If baseline assessments differed significantly between groups, changes from baseline assessments were compared. Comparisons of more than two groups, such as changes over time, were performed using parametric analysis of variance (ANOVA) for repeated measurements (one-way), or the Friedman ANOVA, as appropriate. The smallest differences between placebo and local morphine detectable with a power of 80% and a type I error of 5% were calculated for all measurements at all time points. *P*-values below 0.05 were considered statistically significant.

Results

Baseline assessments did not differ significantly except for heat pain detection thresholds. Because thresholds were higher for placebo than for systemic treatment (P=0.01), and higher for systemic than for local treatment (P=0.03), further comparisons between treatments for heat pain detection thresholds were performed using changes from baseline assessments. Post-drug assessments (performed pre-burn) differed significantly for two measurements: mechanical pain outside the burn area was higher for local than for systemic treatment (P=0.01); and the pain response to heat (45°C, 5 s) was more intense for local than for placebo treatment (P=0.04). The pain response (VAS 0–100) to the burn was not significantly altered by either systemic or local morphine treatment (Fig. 1). In 11 out of 18 subjects, allodynia developed around the burn injury area when tested 4–6 min after start of the burn. The areas of allodynia were larger with local than systemic treatment (P=0.04). Neither local nor systemic morphine treatment

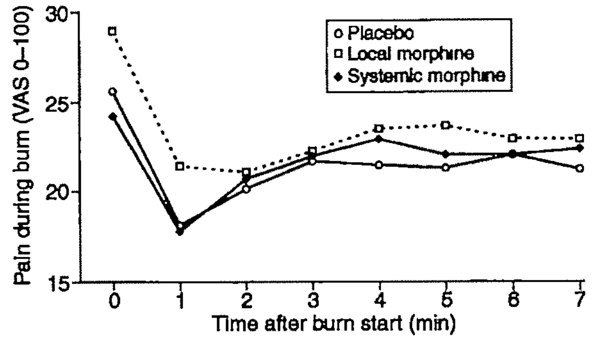

Fig 1 Pain during burn (47°C, 7 min). Verbal descriptors were added to the VAS at 2 mm (weak pain), 8 mm (mild pain), 18 mm (moderate pain), 39 mm (intense pain) and 74 mm (very intense pain). The pain response to the burn was not significantly altered by either systemic or local morphine treatment

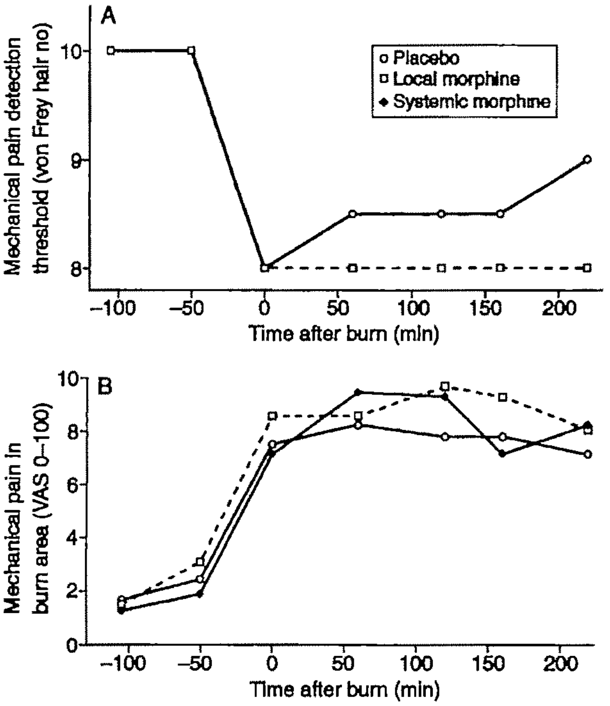

Fig 2 Mechanical pain detection thresholds (medians, A) and mechanical pain in the burned area (medians, B) Neither the pain threshold nor the suprathreshold pain response was significantly altered by local morphine compared with systemic morphine or placebo For illustrative reasons (A) does not show systemic treatment, due to identical line plots of local and systemic treatment.

changed the areas of allodynia significantly compared with placebo.

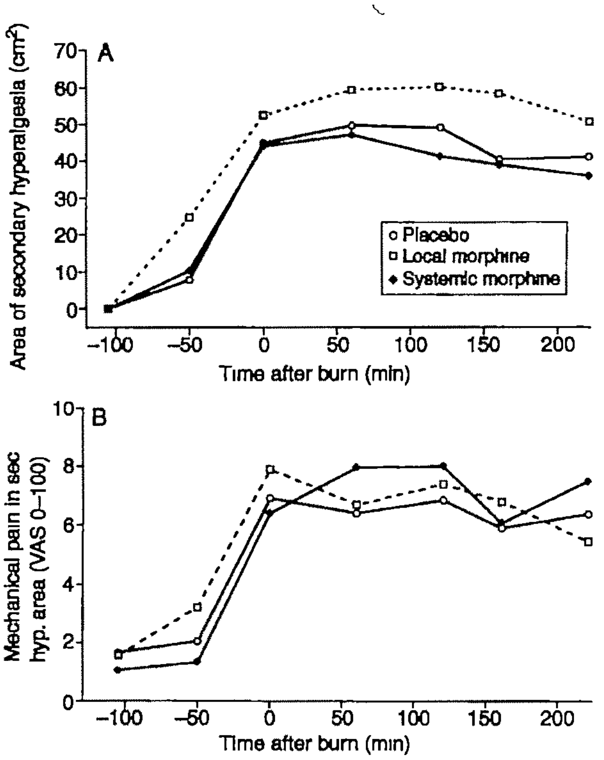

Fig 3 Area of secondary hyperalgesia (medians, A) and mechanical pain in the secondary hyperalgesic area (medians, B) Burns treated with local morphine developed larger areas of hyperalgesia than burns treated with systemic morphine 0–2 h after the burn injury (P=0.03). Also after naloxone injection, burns treated with local morphine showed larger areas of secondary hyperalgesia than burns treated with systemic morphine or placebo (P<0.04). Pain response to mechanical stimuli in the area of secondary hyperalgesia showed no significant differences between local, systemic or placebo treatment.

The burns decreased mechanical pain thresholds ($P<10^{-5}$) and increased pain responses to mechanical stimuli within the site of injury ($P<10^{-5}$, Fig. 2A and B). Neither the pain threshold nor the suprathreshold pain response was significantly altered by local morphine compared with systemic morphine or placebo. The burn produced significant areas of hyperalgesia to punctate mechanical stimuli around the injury ($P<10^{-5}$), and the burns increased the pain responses to mechanical stimuli in the area of secondary hyperalgesia ($P<10^{-5}$, Fig. 3A and B). Burns treated with local morphine developed larger areas of secondary hyperalgesia than when treated with systemic morphine 0–2 h after the burn injury (P=0.03). After naloxone injection, burns treated with local morphine showed larger areas of hyperalgesia than both systemic morphine and placebo treatments (P<0.04). Pain responses to mechanical stimuli in the area of secondary hyperalgesia showed no significant differences between local, systemic or placebo treatment.

Pain responses to 45°C (5 s) were increased by the burn ($P<10^{-5}$), and heat pain thresholds were decreased in the burn area when treated with placebo or systemic morphine (P<0.04), whereas thresholds were not significantly affected by the burn when treated with local morphine. However, the heat pain threshold was not significantly increased by local morphine compared with systemic morphine or placebo, nor was the pain during the brief (5 s) heat stimuli reduced by local morphine compared with systemic morphine or placebo (Fig. 4A and B).

The burn induced an increase in warm detection thresholds for all treatments ($P<10^{-5}$, Fig. 5A). Cold detection thresholds were only significantly increased by the burn, when treated with local morphine (P=0.007, Fig. 5B).

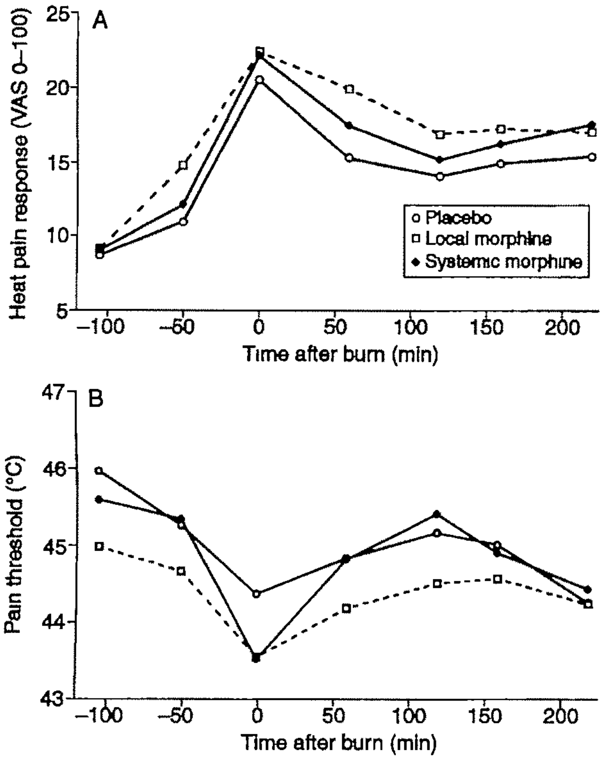

Fig 4 Pain response to a heat stimulus of 45°C (medians, A) and heat pain thresholds (means, B). The pain during the brief (5 s) heat stimuli was not reduced by local morphine, nor was the heat pain threshold significantly increased by local morphine compared with systemic morphine or placebo.

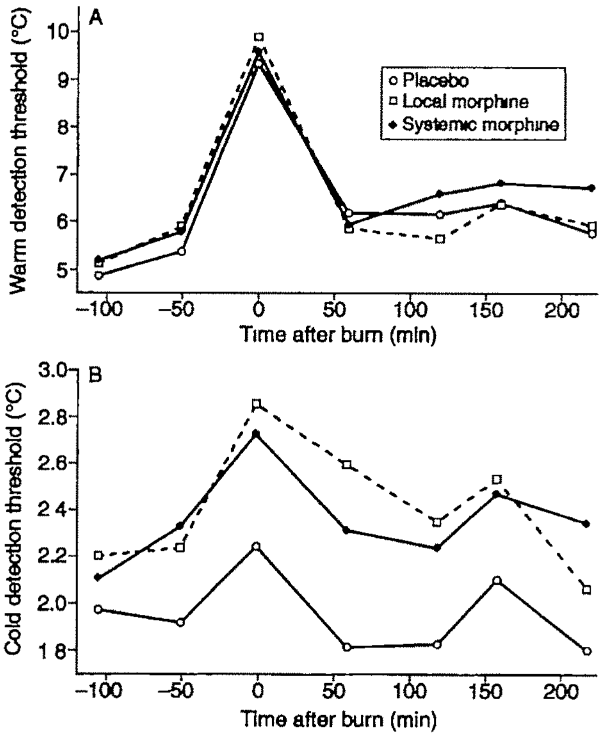

Fig 5 Warm detection thresholds (means, A) and cold detection thresholds (medians, B) Neither warm nor cold detection showed significant differences between treatments 0–2 h after the burn injury After naloxone injections both warm and cold detection thresholds were significantly higher with systemic morphine compared with placebo (*P*=0.03). None of the other treatments differed significantly

Table 1 The smallest detectable differences between placebo and local morphine with a power of 80% and a type 1 error of 5% The values are the means of seven observation times (baseline, post-drug, 0, 1 and 2 h after heat injury, and 30 and 90 min after naloxone injection)

Pain during burn	**Warm detection threshold**	**Cold detection threshold**	**Heat pain threshold**	**Heat pain response to 45°C for 5 s**	**Mechanical pain in burn area**	**Mechanical pain threshold**	**Area of secondary hyperalgesia**	**Mechanical pain in zone of secondary hyperalgesia**
(VAS· 0–100)	(°C)	(°C)	(°C)	(VAS· 0–100)	(VAS· 0–100)	(von Frey no)	(cm^2)	(VAS 0–100)
6.6	0.9	0.8	1.9	5.7	3.9	0.9	15.5	2.7

Neither warm nor cold detection showed significant differences between treatments before or 0–2 h after the burn injury.

Subjects evaluated the pain caused by the injection using a VAS-score. Saline injections were rated with a mean score on the VAS of 31, morphine with a mean score of 35 and naloxone with a mean score of 41. Pain response to injection was significantly more intense for morphine than for saline injections ($P<0.02$).

All side effects (euphoria, nausea, bluntness, headache, dizziness, confusion, feeling of being drunk, itching and restlessness) were reported except headache. However, most side effects were reported by only one–three subjects out of 18 and were rated as weak. One exception was itching which was reported by seven subjects of which two rated the intensity of itching as moderate and one rated it as marked. When saline was injected only one subject reported dizziness. No other side effects related to saline were reported.

The smallest differences between placebo and local morphine detectable at single time points are presented in Table 1. The values are the means of seven observation times (baseline, post-drug, 0, 1 and 2 h after heat injury, and 30 and 90 min after naloxone injection).

Discussion

We examined the antinociceptive effect of morphine infiltrated s.c. in a human model of acute inflammatory pain based on a standardized burn injury in healthy volunteers. Our results suggest no antinociceptive effect of morphine, as none of our assessments showed significantly decreased pain intensity or increased pain thresholds when treated with local morphine compared with systemic morphine or placebo. In contrast, local morphine may have contributed to hyperalgesia as the areas of secondary hyperalgesia were larger when treated with local morphine compared with systemic morphine. The finding that local naloxone did not change hyperalgesia supports the lack of a peripheral analgesic effect of morphine. Further, we were not able to detect any analgesic action of the low dose of morphine (2 mg) as none of the pain assessments was significantly different between placebo and systemic morphine, and side effects rated as weak were only observed in one–three of 18 subjects. Only warm detection thresholds increased when treated with systemic morphine compared with placebo. In summary, peripheral morphine administration did not reduce pain significantly either in normal skin or in hyperalgesic skin.

Our results may have been influenced by the pH of the morphine solution. The pH of morphine was 4.1, naloxone 4.3 and saline 5.6. Injection of morphine induced a significantly higher pain score compared with saline injections ($P<0.02$), which may be explained by the lower pH. The acidic morphine solution may be local irritating and increased sensitization of nociceptors in the burn area, thereby counteracting the possible antinociceptive effect of morphine. However, the morphine solution used was the one generally applied for clinical use. Further, we cannot exclude a minor analgesic effect of morphine, as we were able to detect an ~40% difference between the overall mean of measurements between treatments and with a power of 80% for most measurements.

Our results are not contradictory to the clinical studies wherein extra-articular administration of opioid had no relevant effect,[6] or the studies of intra-articular administration which have shown variable effects.[5] However, our results do not exclude a late (e.g. >8 h) analgesic effect of peripheral morphine.[10] In other experimental human pain models (capsaicin,[11] thermal stimulation,[12] propofol injection pain[13]), the peripheral analgesic effects of opioids have also been debatable, as only the capsaicin model showed a peripheral analgesic effect.[11]

In conclusion, our results cannot verify acute antinociceptive effects of peripheral morphine in this model of acute inflammatory pain.

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References

1. Stein C. The control of pain in peripheral tissue by opioids. *N Engl J Med.* 1995; **332**: 1685–90
2. Stein C, Schäfer M, Hassan AH. Peripheral opioid receptors. *Ann Med* 1995; **27**: 219–21
3. Fields HL, Emson PC, Leigh BK, Gilbert RF, Iversen LL. Multiple opiate receptor sites on primary afferent fibres. *Nature* 1980; **284**: 351–3
4. Hassan AH, Pzewlocki R, Herz A, Stein C. Dynorphin, a preferential ligand for kappa-opioid receptors, is present in nerve fibers and immune cells within inflamed tissue of the rat. *Neurosci Lett* 1992; **140**: 85–8
5. Kalso E, Tramèr MR, Carroll D, McQuay HJ, Moore RA. Pain relief from intra-articular morphine after knee surgery: a qualitative systematic review. *Pain* 1997; **71**: 127–34
6. Picard PR, Tramèr MR, McQuay HJ, Moore RA. Analgesic efficacy of peripheral opioids (all except intra-articular): a qualitative systematic review of randomised controlled trials. *Pain* 1997; **72**: 309–18
7. Moiniche S, Dahl JB, Kehlet H. Peripheral antinociceptive effects of morphine after burn injury. *Acta Anaesthesiol Scand* 1993; **37**: 710–2
8. Pedersen JL, Kehlet H. Hyperalgesia in a human model of acute inflammatory pain: a methodological study *Pain* 1998; **74**: 139–51
9. Altman DG. *Practical Statistics for Medical Research.* London: Chapman & Hall, 1991
10. Likar R, Sittl R, Gragger K, *et al.* Peripheral morphine analgesia in dental surgery. *Pain* 1998; **76**: 145–50
11. Kinnman E, Nygårds E, Hansson P. Peripherally administrated morphine attenuates capsaicin-induced mechanical hypersensitivity in humans. *Anesth Analg* 1997; **84**: 595–9
12. Atanassoff PG, Brull SJ, Printsev Y, Silverman DG. The effect of intradermal administration of lidocaine and morphine on the response to thermal stimulation. *Anesth Analg* 1997; **84**: 1340–3
13. Pang WW, Mok MS, Huang S, Hwang MH. Analgesic effect of fentanyl, morphine, meperidine and lidocaine in peripheral veins: a comparative study. *Anesth Analg* 1998; **86**: 382–6

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Efficacy and respiratory effects of low-dose spinal morphine for postoperative analgesia following knee arthroplasty

P. J. Cole*, D. A. Craske and R. G. Wheatley

The Acute Pain Management Unit, York District Hospital, Wigginton Road, York YO3 7HE, UK

**Corresponding author*

A randomized, double-blind study of 38 patients undergoing total knee replacement was undertaken to compare the efficacy and respiratory effects of low-dose spinal morphine and patient-controlled i.v. morphine against patient-controlled i.v. morphine alone. Patients received either morphine 0.3 mg or saline 0.3 ml with 0.5% heavy spinal bupivacaine 2–2.5 ml. Respiratory effects were measured continuously for 14 h postoperatively with an Edentec 3711 respiratory monitor. There was an improvement in pain relief in the intrathecal morphine group, with significantly lower median VAS pain scores on movement at 4 h (0 (median 0–1.5) *vs* 5 (1.25–7.75) $P<0.01$), 12 h (2 (1–5) *vs* 6 (3–8) $P<0.01$) and 24 h (3 (1–5) *vs* 5 (3–7) $P<0.05$) postoperatively, despite using significantly less patient-controlled morphine (20 mg (10.25–26.25) *vs* 38.5 mg (27–51) $P<0.01$) in the first 24 h. There was a small but statistically significant reduction in the median oxygen saturation (Sp_{O_2}) in the intrathecal morphine group 97 (95–99)% compared with the placebo group 99 (97–99)% ($P<0.05$). Although marked disturbances in respiratory pattern were observed in both groups, none of the patients in the study had severe hypoxaemia (Sp_{O_2} <85% >6 min h^{-1}) and there was no significant difference in the incidence of mild (Sp_{O_2} <94% >12 min h^{-1}) or moderate (Sp_{O_2} <90% >12 min h^{-1}) hypoxaemia or in the incidence of episodes of apnoea or hypopnoea in the two groups.

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Intrathecal opioids have been shown to provide effective analgesia in a variety of surgical settings[1 2] since the introduction of the technique into clinical practice in 1979.[3] The advantage of spinally administered opioids is that prolonged analgesia can be provided using a single injection at the time of surgery without the need for cumbersome and expensive pumps in the postoperative period. However, the use of this technique has been limited by a high incidence of opioid-related side effects including nausea, pruritus and urinary retention, and the fear of respiratory depression, which may be delayed in onset. In an attempt to limit major and minor opioid side effects, the use of low-dose spinal opioids has been advocated.[4–6] When using low doses there are concerns about the appropriate choice of rescue analgesia if patients have ineffective pain relief. Although studies using intrathecal opioids have demonstrated improved analgesia, there have been a limited number of studies that assess their respiratory effects.[7]

The aim of this study was to investigate whether the combination of low-dose (0.3 mg) intrathecal morphine and patient-controlled i.v. morphine provides more effective analgesia than patient-controlled i.v. morphine alone in patients undergoing knee arthroplasty. A secondary aim was to investigate the respiratory effects of the combination of intrathecal morphine and patient-controlled i.v. morphine as rescue analgesia.

Methods

After obtaining Hospital Ethics Committee approval and informed patient consent, we studied 38 ASA 1 or 2 patients scheduled for unilateral knee arthroplasty, in a prospective, randomized, double-blind, placebo-controlled study

Patients undergoing knee arthroplasty were chosen for this study because audit from our acute pain team has consistently shown that these patients have high analgesic requirements and require early mobilization.

Patients in whom either non-steroidal anti-inflammatory drugs or spinal anaesthesia were contraindicated were excluded from the study.

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The anaesthetic management of all patients was standardized. Spinal anaesthesia was undertaken using a mixture of 0.5% heavy bupivacaine 2–2.5 ml plus a pharmacy-prepared solution of morphine or saline, which was allocated on a double-blind randomized basis by pharmacy, using a computer-generated random number system. The randomization was stratified to ensure that morning and afternoon cases were divided equally between the two groups.

Patients received either morphine 0.3 mg (0.3 ml from a 2-ml ampoule of 1 mg ml^{-1} preservative-free morphine), or normal saline 0.3 ml (0.3 ml from a 2 ml 0.9% sodium chloride solution) in addition to the bupivacaine in their spinal anaesthetic. General anaesthesia was induced in unpremedicated patients with propofol (1–3 mg kg^{-1}) and fentanyl (0–1 μg kg^{-1}) at the anaesthetist's discretion. Maintenance of anaesthesia was provided with oxygen, nitrous oxide and enflurane in patients breathing spontaneously through a laryngeal mask airway.

In addition to the spinal injection, postoperative analgesia consisted of diclofenac 50 mg every 8 h (PO or PR). Patients were allowed to self-administer i.v. morphine via a patient-controlled analgesia system (Graseby 9300 model) in 1 mg boluses with a 5-min lockout period. Metoclopramide was routinely prescribed for postoperative nausea and vomiting. All patients were given oxygen by nasal cannulae at 2 litres min^{-1}, if at any time their oxygen saturation was noted to be 94% or below.

The use of a visual analogue scale was described at the preoperative visit and the effectiveness of analgesia was measured by visual analogue pain scores on movement (VASm 0–10) at 4, 12 and 24 h. Patients were also asked to give a verbal rating score for satisfaction with the quality of analgesia (poor, fair, adequate, good, excellent), and pain severity (absent, mild, discomforting, distressing, excruciating) for the 24-h period. In addition, the PCA 24 h morphine consumption was recorded.

Respiration was monitored continuously using the Edentec model 3711 digital recorder (Edentec 3711, Nellcor, Eden Prairie, MN, USA) for 1 h preoperatively for a baseline reading, and then for 13–14 h after the patient had returned to the orthopaedic ward postoperatively. This digital recorder comprises a lightweight portable recorder, with non-invasive probes attached to the subject, continuously measuring nasal airflow, chest impedance and pulse oximetry. Chest impedance and heart rate were recorded by attaching two electrodes to each side of the chest (mid axillary line at T4–5). Chest wall movement was measured by passing a constant current through the chest giving a measure of impedance. Nasal airflow was measured by a thermistor attached between the upper lip and nose.

All Edentec respiratory data were downloaded onto a desktop computer. Each tracing was assessed in 10-min epochs by two of the authors (P.C., D.C.) in a blinded fashion. These data were edited to exclude obvious artefact recordings, which included non-physiological hypoxaemia, interference due to patient movement and/or disconnection from the recorder. The edited data were then analysed using an ETS 2.0 software program.

An apnoea event starts when the airflow stays between +5% and −5% of baseline for at least 10 s, and ends when the airflow is greater than 5% or less than −5%. A hypopnoea event starts when the trace amplitude is less than 50% of the average amplitude over the previous 2 min and stays at or below this level for at least 10 s. The event ends as soon as the amplitude increases above 50% of the average amplitude.[8] Frequencies of events were calculated per hour of recording. Studies with less than 4 h of recorded data were regarded as technically unsatisfactory and rejected. The respiratory distress index (RDI) is the sum of apnoea and hypopnoea events per hour. An RDI greater than 30 is said to be diagnostic of sleep apnoea/hypopnoea syndrome requiring treatment.[8]

Hypoxaemia was classified by previously defined criteria[9] as mild when the Sp_{O_2} was <94% >12 min h^{-1}, moderate when the Sp_{O_2} <90% >12 min h^{-1} and severe when the Sp_{O_2} <85% >6 min h^{-1}. The mean saturations and the percentage time spent below a saturation of 95% during the study period for each patient were also recorded.

Measurement of oxygen saturation, sedation scoring (0=none, patient alert; 1=mild, occasionally drowsy, easy to arouse; 2=moderate, frequently drowsy, easy to arouse; 3=severe; somnolent, difficult to arouse), respiratory rate and visual analogue score for pain were recorded on the ward at hourly intervals for the first 4 h and then every 4 h thereafter. The incidence of nausea or pruritus requiring treatment was noted.

Previously collected audit data on patients who had received a spinal anaesthetic with bupivacaine alone and a morphine PCA following knee arthroplasty had shown that the mean morphine consumption was 40 (SD 16) mg. Assuming a clinically significant reduction in morphine consumption of 20 mg, it was calculated[10] that 30 patients (15 pairs) would be required to have a 90% power of detecting a 50% reduction in 24 h morphine consumption at a significance level of 0.05.

Data were analysed by using the SPSS statistics package (version 8). Mann–Whitney and chi-squared tests were used for the non-parametric data, and an unpaired Student's *t*-test for the patient characteristics. A value of $P<0.05$ was regarded as statistically significant.

Results

Thirty-eight patients completed the study. Two patients were excluded as an incorrect dose of intrathecal drug was administered to one and premedication was given to the second. Due to software problems with the Edentec monitor and patient non-compliance, a further four patients had incomplete respiratory data for analysis, but their data on morphine consumption were included.

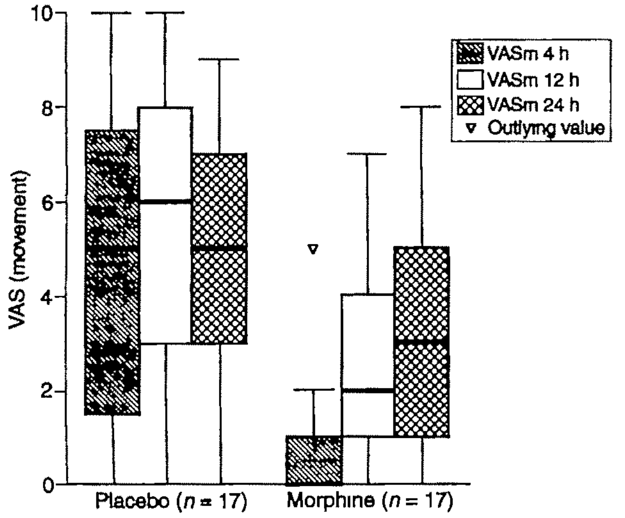

Fig 1 Box plot of visual analogue score on movement (VASm) scores at 4, 12 and 24 h postsurgery. Boxes represent interquartile range, horizontal lines in the boxes represent median values, and error bars the range The VASm scores were significantly reduced at 4 (P<0.01), 12 (P=0.01) and 24 (P<0.05) h in the intrathecal morphine group when compared with the intrathecal saline group Open inverted triangle represents an outlying value.

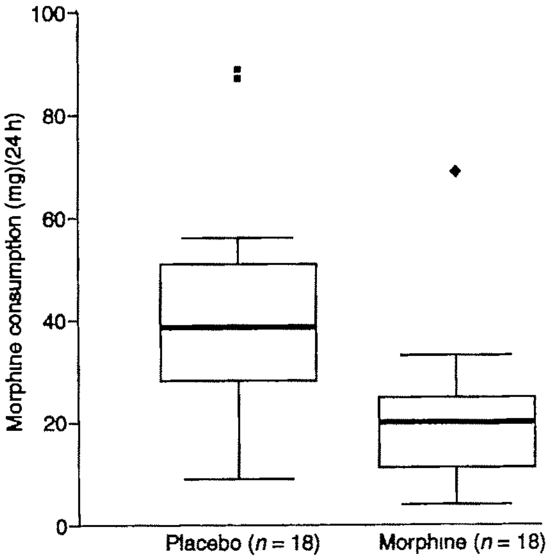

Fig 2 Box plot of i.v PCA morphine consumption in the first 24 h postsurgery in the intrathecal morphine and intrathecal saline (placebo) groups. Boxes represent interquartile range, horizontal lines in the boxes represent median values, and error bars the range There is a significant difference between the intrathecal morphine and intrathecal placebo groups (P<0.01). Closed diamond and closed square represent outlying values

Patient characteristics were similar between the two groups. Mean (SD) age, body weight and height were 70.3 (9.9) yr, 82.3 (15.7) kg and 1.7 (0.1) m, and 71.3 (7.6) yr, 80.5 (14.3) kg and 1.7 (0.1) m in the intrathecal morphine and intrathecal saline groups, respectively.

The preoperative baseline respiratory monitoring showed median saturations (interquartile range) of 98.5 (96–99)% in the morphine group and 98.5 (97–99)% in the control group.

Patients in the intrathecal morphine group had significantly lower VASm pain scores on movement at 4, 12 and 24 h (Fig. 1), and used a significantly lower dose of patient-controlled i.v. morphine in the first 24 h after surgery (Fig. 2).

Although more patients in the intrathecal morphine group scored the severity of their pain as mild or absent and more patients in this group required treatment for emesis, these differences were not statistically significant. There was no significant difference between the two groups in the incidence of pruritus or their verbal rating of satisfaction (Table 1).

When comparing the apnoea and hypopnoea episodes, there was no significant difference between the two groups in the median RDI or in the incidence of those with a respiratory distress index >30 (Table 2). Patients in both groups had disordered respiratory patterns with episodes of central and obstructive apnoea.

The median values of the mean saturations in the postoperative period between the two groups were compared and were significantly lower in the intrathecal morphine group compared with the intrathecal saline group. Using previously defined criteria,[9] 5/17 patients in the intrathecal morphine group could be classified as mildly hypoxaemic and 1/17 as moderately hypoxaemic during the study period. In the saline group, 3/15 subjects showed mild hypoxaemia. However, this difference was not statistically significant. No patients had severe hypoxaemia using these criteria.

Although patients in the intrathecal morphine group spent a median of 10% of their time with a saturation below 95% compared with a median of 3% in the placebo group, this was not statistically significant.

Discussion

This study has achieved the primary aim of demonstrating that, following knee arthroplasty, intrathecal morphine 0.3 mg followed by patient-controlled i.v. morphine, improves postoperative analgesia and reduces i.v. morphine consumption compared with patient-controlled i.v. morphine alone. This confirms earlier studies on the quality of analgesia after Caesarean section[11–14] and hip surgery.[15]

Whilst this combination of intrathecal and patient-controlled i.v. morphine provides effective analgesia, there are concerns in clinical practice about the safety of intrathecal opioids particularly if systemic opioids are used for rescue analgesia. A 17-nation European survey revealed that, except for the UK, morphine was the most commonly used of the long-acting opioids.[16] This initial study used morphine because it has been extensively used, and whatever degree of respiratory depression was seen with intrathecal morphine, respiratory depression would be less

Table 1 Highest sedation score, minor side effects and patient satisfaction/severity during the first 24 h. There was no difference in the median highest sedation scores in the first 24 h between the two groups. Median values and interquartile ranges are shown. The number of patients requiring antiemetic treatment and reporting pruritus was higher in the intrathecal morphine group, but this was not statistically significantly. Patients reported their analgesia as good or excellent, and their pain severity as absent or mild more frequently in the intrathecal morphine group compared with the saline group

	Sedation score	Emesis (treated) (*n*=31)	Pruritus (*n*=29)	Satisfaction (good/excellent) (*n*=32)	Severity (absent/mild) (*n*=31)
Morphine	1 [0–2]	Nine out of 15 (60%)	Four out of 15 (27%)	Nine out of 15 (60%)	12 out of 14 (86%)
Placebo	1 [0–1.5]	Six out of 16 (38%)	Two out of 14 (14%)	Nine out of 17 (53%)	Nine out of 17 (53%)
P-value	NA	0.07	0.65	0.96	0.07

Table 2 Postoperative respiratory data. Median (interquartile range) respiratory distress indices (RDI) and number of patients who had an RDI count >30 are shown, there was no significant difference within these groups. The median values of the mean saturations (interquartile range) (%) show a statistical difference between the two groups*. There were more episodes of hypoxaemia in the intrathecal morphine group compared with the saline group but this did not reach statistical significance. *$P<0.05$

	Morphine group (*n*=17)	Placebo group (*n*=15)	*P*-value
RDI	19 (4–35.5)	13 (3–34)	0.53
RDI count >30	Six out of 17	Five out of 15	0.91
Median Sp_{O_2} (%)	97 (95–99)	99 (97–99)	0.03*
Incidence of mild/moderate hypoxaemia	Six out of 17	Three out of 15	0.36

likely to occur when low doses of more lipid-soluble opioids are administered by the intrathecal route.[7 17]

Due to the dose-dependent nature of respiratory depression,[5] a dose of morphine 0.3 mg was used, based on an earlier dose–response study that showed that this is an effective dose with the fewest side effects.[4] However, more recent studies have shown that lower doses (0.1 mg) are effective for analgesia after Caesarean section[12] and hip replacement surgery.[14]

There have been many reports of respiratory depression following spinal opioids.[7] Previous studies looking at the respiratory effects of intrathecal opioids have used a combination of pulse oximetry, sedation scoring, respiratory rate and invasive arterial blood–gas analysis.[5 7 18]

The availability of relatively simple to use, bedside respiratory monitors allows us to continuously study the ventilatory pattern and oxygenation of patients receiving intrathecal opioids. Although it is often assumed that bedside monitors such as the Edentec are less accurate than conventional sleep studies with polysomnography, this equipment has recently been used to validate the detection of respiratory disturbances in patients with sleep apnoea/hypopnoea syndrome[8] and to investigate patients recovering from major abdominal surgery.[19]

Our study demonstrated that respiratory disturbances occurred in both groups. The pattern of respiratory dysfunction was similar to that previously described following the use of i.v. morphine,[20 21] and included obstructive and central apnoeas.

Although patients in the morphine group spent three times as long with a saturation below 95% and twice as many were classified as 'hypoxaemic patients'; that is they spent greater than 20% of their time with mild or moderate hypoxaemia (85–94%),[9] these differences were not statistically significant. The only statistical difference was between the median oxygen saturations in the two groups. In view of the risks of postoperative hypoxaemia[22] and its potential effects on postoperative morbidity, it was deemed necessary to give patients in this study supplementary oxygen if their oxygen saturations fell below 94%. Because oxygen was not administered to all the study patients, the small but statistically significant difference between the mean saturations (97% and 99%) may not be of clinical significance.

None of the patients in the study met the pre-defined criteria[9] for severe hypoxaemia, that is, spending more than 10% of their time with a saturation below 85%. The only patient in the study who approached this level was a patient in the spinal morphine group who spent 90% of their time with saturation below 95% including 4% of their time below 85%. This would be regarded by most clinicians as a significant level of hypoxaemia.

Because of the low incidence of respiratory depression, a much larger study would be needed to detect or exclude a significantly increased risk with low-dose spinal morphine. Further studies are required into the efficacy and duration of action of more lipid-soluble opioids which are likely to be associated with a lower incidence of respiratory depression.

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References

1 Rawal N. Epidural and spinal agents for postoperative analgesia. *Surg Clinics North Am* 1999; **79**: 313–44

2 Carr DB, Cousins MJ. Spinal route of analgesia: opioids and future options. In: Cousins MJ, Bridenbaugh PO, eds, *Neural Blockade in Clinical Anaesthesia and Management of Pain*, 3rd edn. Philadelphia: Lippincott-Raven, 1998

3 Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. *Anaesthesiology* 1979; **50**: 149–51

4 Sarma VJ, Bostrom UV Intrathecal morphine for the relief of post hysterectomy pain – a double blind dose response study. *Acta Anaesthesiol Scand* 1993; **37**: 223–7

5 Bailey PL, Rhondeau S, Schafer PG *et al.* Dose–response pharmacology of intrathecal morphine in human volunteers. *Anaesthesiology* 1993; **79**: 49–59

6 Jacobson L, Chabal C, Brody MC. A dose–response study of intrathecal morphine: efficacy, duration, optimum dose, and side effects. *Anaesth Analg* 1988; **67**: 1082–8

7 Etches RC, Sandler AN, Daley MD. Respiratory depression and spinal opioids. *Can J Anaesth* 1989; **36**: 165–85

8 Whittle AT, Finch SP, Mortimer IL, MacKay TW, Douglas NJ. Use of home sleep studies for diagnosis of sleep apnoea/hypopnea syndrome. *Thorax* 1997; **52**: 1068–73

9 Wheatley RG, Shepherd D, Jackson IJB, Madej TH, Hunter D. Hypoxaemia and pain relief after upper abdominal surgery: comparison of I.M. and patient controlled analgesia. *Br J Anaesth* 1992; **69**: 558–61

10 Altman DG. How large a sample? Statistics and ethics in medical research. *BMJ* 1980; **281**: 1336–8

11 Swart M, Sewell J, Thomas D. Intrathecal morphine for Caesarean section: an assessment of pain relief, satisfaction and side effects. *Anaesthesia* 1997; **52**: 373–7

12 Palmer CM, Emerson S, Volgoropolous D, Alves D. Dose–response relationship of intrathecal morphine for postcesarean analgesia. *Anesthesiology* 1999; **90**: 437–44

13 Husaini SW, Russell IF. Intrathecal diamorphine compared with morphine for postoperative analgesia after Caesarean section under spinal anaesthesia. *Br J Anaesth* 1998; **81**: 135–9

14 Gerancher JC, Floyd H, Eisanach J. Determination of an effective dose of intrathecal morphine for pain relief after cesarean delivery. *Anesth Analg* 1999; **88**: 346–51

15 Slappendel R, Weber EW, Dirksen R, Gielen MJ, Van Limbeek J. Optimisation of the dose of intrathecal morphine in total hip surgery: a dose finding study. *Anesth Analg* 1999; **88**· 822–6

16 Rawal N, Allvin R. Euro-pain study on acute pain. Epidural and intrathecal opioids for postoperative pain management in Europe – a 17 nation questionnaire study of selected hospitals. *Acta Anaesthesiol Scand* 1996; **40**: 1119–26

17 Hamber EA, Viscomi CM. Intrathecal lipophilic opioids as adjuncts to surgical spinal analgesia. *Reg Anaesth Pain Medicine* 1999; **24**: 255–63

18 Kelly MC, Carabine UA, Mirakhur RK. Intrathecal diamorphine for analgesia after Caesarean section. A dose finding study and assessment of side effects. *Anaesthesia* 1998; **53**: 231–7

19 Rosenberg J, Rasmussen GI, Wojdemann KR, Kirkeby LT, Jorgensen LN, Kehlet H. Ventilatory pattern and associated episodic hypoxaemia in the late postoperative period in the general surgical ward. *Anaesthesia* 1999; **54**: 323–28

20 Jones JG, Jordan C, Scudder C, Rocke DA, Barrowcliffe M. Episodic postoperative oxygen saturation: the value of added oxygen. *J Roy Soc Med* 1985; **78**: 1019–22

21 Catley DM, Thornton C, Jordan C, Lehane JR, Royston D, Jones JG. Pronounced, episodic oxygen desaturation in the postoperative period; its association with ventilatory pattern and analgesic regime. *Anaesthesiology* 1985; **63**: 20–8

22 Reeder MK, Muir AD, Foex P, Goldman MD, Loh L, Smart D. Postoperative myocardial ischaemia: temporal association with nocturnal hypoxaemia. *Br J Anaesthesia* 1991; **67**: 626–31

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How much work is required to puncture dura with Tuohy needles?

M. C. Lewis*, J. P. Lafferty, M. S. Sacks, V. S. Pallares and M. TerRiet

Departments of Anesthesiology, and Biomedical Engineering, Veterans Affairs Medical Center/Jackson Memorial Medical Center, University of Miami, Miami, FL, USA

**Corresponding author: Anesthesiology Service (139), Veterans Affairs Medical Center, 1201 NW 16th Street, Miami, FL 33125, USA*

The effects of needle bevel orientation and cerebrospinal fluid (CSF) pressure on dural displacement and force required to penetrate cadaveric dura were studied using 40 samples. A constant hydrostatic pressure was applied to the subdural surface, either high or low, simulating the sitting and lateral positions. A 17-gauge Tuohy needle was advanced through the dura with the bevel oriented parallel or perpendicular to dural fibres. Travel distance and peak force at which dural penetration occurred were measured under both pressure conditions. The work required to produce dural penetration was calculated. Greater force and work were required to penetrate dura in the perpendicular orientation ($P<0.05$), regardless of the subdural pressure exerted. Dural displacement was similar under both pressure conditions.

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Keywords: dural leak, dural penetration, dural tenting; epidural needle orientation; position simulation

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Headache occurs in up to 85% of patients following dural puncture with a 17-gauge Tuohy needle,[1] causing significant perioperative morbidity. Some of the differences in the force required for dural penetration with different bevel positions and dural stress may be accounted for in terms of the dura's biomechanical properties.[2] Dural bulging may occur in the sitting position, as cerebrospinal fluid (CSF) pressures are higher,[3] possibly increasing the tendency for puncture, as compared with the lateral or prone positions. Data derived from spinal anaesthesia studies[4] have led to the practice of entering the epidural space with the needle positioned parallel to the fibres,[5] and then rotating the needle to insert the epidural catheter. CSF leakage would be minimized[1] if dural puncture occurred with the needle bevel oriented parallel to the fibre direction. This study was designed to evaluate whether bevel orientation or patient position alters the force necessary to produce dural puncture. In addition, we examined the effect of bevel orientation and patient position on maximal dural tenting before dural penetration. The work (force×dural displacement) required to produce dural penetration was calculated for all conditions.

Methods

Ten posterior lumbar cadaveric dura samples were harvested, trimmed to strips, and then stored in normal saline at 3°C until use. All samples were obtained from adults.

A neoprene-O-ring placed on a metal platform (Fig. 1) was used to hold dura tightly, and pressure was applied to the subdural surface. Two pressures were used: 65 cm H_2O (which simulates the sitting position) and 5 cm H_2O (which simulates the supine or lateral position).[1 3] The sitting simulation pressure was slightly greater than that demonstrated *in vivo* in the literature, so that we could see bulging of the dural sample. A water manometer was used to measure these pressures, which were held constant throughout each experiment.

In order to achieve appropriately blunted needles for the experimental situation, 17-gauge Tuohy needles, which had been used previously in one single atraumatic epidural catheter insertion, were collected. Such bluntness simulates changes that occur in the *in vivo* situation due to passage through tissues prior to reaching the dura. Subsequently, each needle was used for eight dural punctures (two punctures in two dural strips, at each of the four simulations), and then discarded.

A materials testing machine (Instron Model 1000 Canton, MA, USA) was used to manipulate the Tuohy needle on all dural samples. This device is capable of advancing the needle at 20 mm min^{-1}, while measuring travel distance (i.e. dural tenting), resistance and the peak force required for dural penetration.

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Four conditions were tested in each of the dural strips, measuring force and total travel before penetration in each of these simulations.

1. Bevel parallel to the longitudinal fibres, supine position simulation.
2. Bevel parallel to the longitudinal fibres, sitting position simulation.
3. Bevel perpendicular to the longitudinal fibres, supine position simulation.

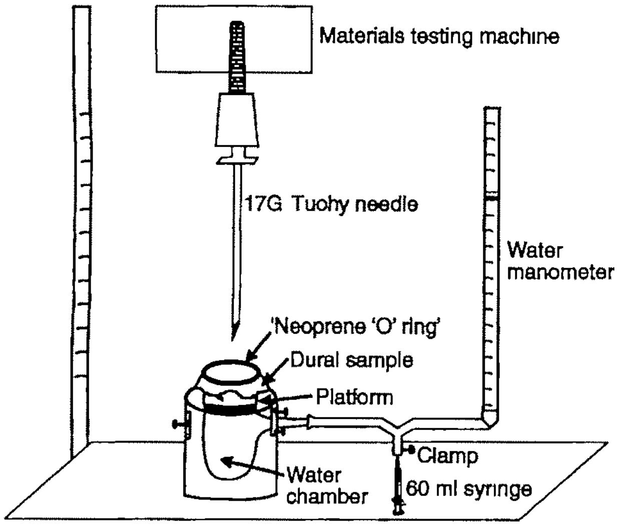

Fig 1 The dural sample is mounted on a metal platform, and held in position by a neoprene-O-ring. Constant pressure is applied to the subarachnoid surface using a water manometer The machine advances the needle and is capable of measuring the total distance travelled and the peak force at the point of dural penetration

4. Bevel perpendicular to the longitudinal fibres, sitting position simulation.

Data were analysed using the pooled *t*-test with $P<0.05$ being considered significant.

A total of 10 dural samples was examined, under the four conditions outlined above; the total number was 40 simulations. Samples with artefacts in the tracings, or accidental puncture of the dura before measurement were excluded. Work required for dural penetration in each test was calculated using the data the force needed for dural penetration, and measurement of needle travel distance (work=force×distance).

Results

A typical tracing obtained from the Instron 1000 is illustrated in Fig. 2. A mean (SEM) of 5.66 (1.21) Newtons (100 g=0.98 N) was required to penetrate the dura with the bevel oriented parallel in the supine simulation and 5.50 (1.33) N in the sitting simulation (NS) (Table 1). When the needle bevel was oriented perpendicularly to dura fibres, a 35% greater force was required in the supine simulation (7.66 (2.47) N). In the sitting simulation, a force of 7.39 (2.06) N was required to pierce the dura. This is 1.89 N more force than was required in the parallel orientation, sitting position (5.50 (1.33) N). The force required for dural penetration with perpendicular orientation in both simulations was significantly greater than that of parallel orientation in equivalent simulations ($P<0.05$).

The mean peak travel (dural displacement prior to penetration) was 0.33 cm (Table 2). This did not differ in

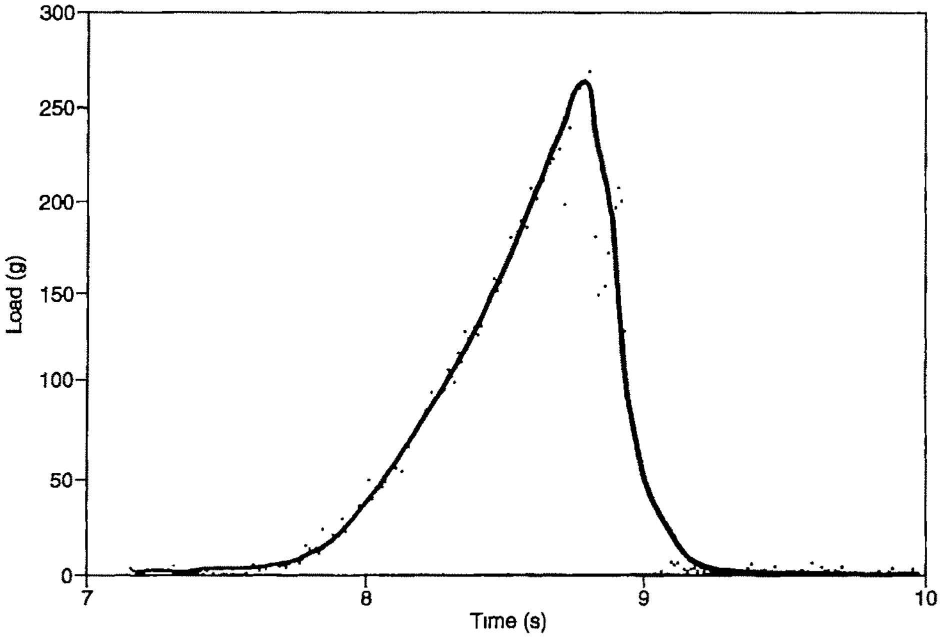

Fig 2 Graph of load (g) (100 g=0 98 N) plotted against time (s) Maximum load is represented by the peak of the graph Because the tracing is at a speed of 20 mm min^{-1} one can calculate the maximum dural displacement by measuring the width of the displacement curve (s) and calculating the distance travelled by the needle in that time. Note the abrupt downward-swing of the tracing on dural penetration

the two patient position simulations or with bevel orientation ($P > 0.05$).

The work at maximum load is obtained from measuring the area under the force versus maximum displacement curve. Table 3 summarizes the data for work at maximum load for all conditions. In the parallel orientation, supine simulation, the work at maximum load was 52.83 (20.39) N mm^{-1} which did not differ from the sitting simulation. However, this value was greater in the perpendicular orientation at both position simulations ($P < 0.05$).

In eight experiments using the parallel orientation, an 'early leak' was noted prior to dural penetration, that is fluid was noted on the epidural surface around the needle tip prior to puncture. This was not seen, however, with the needle oriented in the perpendicular plane.

Discussion

The product of the force applied to a body and its displacement is termed work, which is represented by the area under the force versus dural displacement curve. Classically, most lumbar dural elastic fibres were thought to run in a longitudinal direction,[2,6] however, recent studies have questioned this representation.[7] In the classical model, fewer fibres are cut with the parallel as compared with the perpendicular orientation,[8] and less work may be required for dural penetration. Our data show that work was significantly increased in the perpendicular as compared to the parallel orientation ($P < 0.05$), indicating that greater force was required to penetrate the dura. The practice of entering the epidural space with the needle oriented parallel to the fibres is challenged by this finding. Puncture size made by a needle with this orientation may be smaller, but less force would be necessary for dural penetration.

Table 1 Force (Newtons) required to penetrate the dura All values are mean (SEM) Greater force was required to penetrate the dura with the needle orientated perpendicular to the fibre direction, in both pressure conditions ($P < 0.05$) In both needle orientations there was no difference within the orientation between the sitting and supine conditions

	Bevel orientation	
Position orientation	**Parallel**	**Perpendicular**
Supine (N)	5.66 (1.21)	7.66 (2.47)
Sitting	5.50 (1.33)	7.39 (2.06)

Table 2 Travel (cm) at maximum load prior to dural puncture This value represents dural displacement. All values are mean (SEM) No significant difference

	Bevel orientation	
Position simulation	**Parallel**	**Perpendicular**
Supine (cm)	0.34 (0.16)	0.31 (0.14)
Sitting	0.32 (0.10)	0.31 (0.11)

Table 3 Work (N mm^{-1}) at maximum load All values are mean (SEM). This value is greater ($P < 0.05$) for the perpendicular orientation compared to the parallel, both in the supine and the sitting simulation. There is no significant difference within the needle orientation groups for different position simulations

	Bevel orientation	
Position simulation	**Parallel**	**Perpendicular**
Supine (N mm^{-1})	52.8 (20.4)	119.3 (65.0)
Sitting	54.6 (25.2)	100.7 (62.5)

The rationale for using the parallel bevel orientation to minimize post-spinal headache came from studies using spinal needles,[4] where the aim is to minimize leakage of CSF and the development of post-spinal headache. In epidural anaesthesia, the aim is to avoid a dural tear and therefore prevent CSF leakage. Our data show that when the needle bevel is orientated parallel to the dural fibre direction less force is required to produce perforation. If an epidural needle is introduced into the peridural space with the longitudinal orientation of the bevel, then it must be rotated 90° before introducing the catheter. Such a manoeuvre may increase further the likelihood of tearing the dura.[9] Therefore, the perpendicular bevel orientation of the Tuohy needle is possibly a technique to avoid such dural tears, and what could be a potentially severe headache from a 17-gauge needle.[1]

Clinical studies have failed to identify an increased risk of dural puncture with the parallel as compared with perpendicular needle bevel orientation.[5] It may be that the differences in penetration between the *in vitro* and *in vivo* condition can be accounted for by the resting tension of the dura. Alternatively, the difference between the clinical situation and our findings may be produced by the experimental method. The needle was advanced on the dural sample at a speed of 20 mm min^{-1}. At this slow speed the force required to penetrate the dura may be exaggerated. In addition, the speed of advancement is constant in our experiment. The clinical situation may be marked by variations in the speed of advancement, and the accidental puncture may be related to uncontrolled rapid movement of the needle.

There was no difference in the force producing dural penetrations within needle orientations regardless of the position simulations. We had expected the higher pressure in the sitting position to decrease the force required to puncture the dura. The dura was observed to bulge when pressure was added. Loose lateral fixation of the dura to the bony canal may exaggerate this change *in vivo*, thus the lack of position effect may be related to the experimental method.

The peak travel data suggest that the mechanisms of dural puncture may differ from the presently accepted theory. In our model, when the Tuohy needle was advanced through the centre of the dural sample, it could be displaced 0.35 cm before penetration. Dura is contained within the vertebral canal. The antero-posterior (A-P) diameter is 1.3 cm, whereas the widest transverse diameter between the inter vertebral foramina is 2.2 cm.[10] At the L2 level, the inter vertebral foramina are posterior to a frontal plane passing through the midpoint of the A-P diameter. This means that the dura is not tethered at the posterior aspect of the vertebral canal, but at its midpoint just 0.6–0.7 cm from the anterior wall of the canal. If our dural samples are displaced 0.35 cm, the average lumbar dura at its widest point (2.2 cm) would probably 'tent' more than this. By applying proportionality it may be assumed that dura can be displaced 0.77 cm *in vivo*. Because the dura is tethered only 0.6 mm from the anterior canal wall, it would be impaled prior to being stretched maximally. This is supported by the work of Holloway and Telford,[11] who found that following identification of the epidural space, the needle was advanced 1–1.5 cm prior to obtaining CSF flow in 75% of patients. This would place the needle tip at the anterior limit of the vertebral canal.

In eight experiments with the needle oriented parallel to the fibres, an 'early leak' was noted (i.e. water was noted on the epidural surface prior to actual dural penetration). This may be due to the needle separating the fibres, allowing for some fluid leakage prior to the formation of an actual tract.

In conclusion, our data indicate that more work is required to puncture the dura with the bevel oriented perpendicular to the longitudinal axis. This supports our contention that it may be safer to enter the epidural space with a perpendicularly oriented needle. An 'early leak' phenomenon was observed with the needle oriented parallel to the fibres. The clinical significance of this observation and whether it plays a role in the development of postdural headache in the absence of an observable penetration requires further study.

References

1 Brownbridge P. The management of headache following accidental dural puncture in obstetric patients. *Anaesth Intens Care* 1983; **11**: 4–11

2 Patin DJ, Eckstein EC, Harum K, Pallares VS. Anatomy and biomedical properties of human lumbar dura matter. *Anesth Analg* 1993; **76**: 5535–40

3 Kunkle CE, Ray BS, Wolff H. Experimental studies of headache. Analysis of headache associated with changes in intracranial pressure. *Arch Neurol Psychiatr* 1943; **49**: 323–58

4 Mihic DN. Postspinal headache and the relationship of needle bevel to longitudinal dural fibers. *Reg Anesth* 1985; **10**: 76–81

5 Norris MC, Leighton B, DeSimone CA. Needle bevel direction and headache after inadvertent dural puncture. *Anesthesiology* 1989; **70**: 729–31

6 Fink BR, Walker S. Orientation of fibers in human dorsal dural matter in relationship to lumbar puncture. *Anesth Analg* 1989; **69**: 768–72

7 Dittmann M, Reina MA, Lopez Garcia A. New results in visualization of the dura mater spinalis by scanning electron microscopy. *Anaesthesist* 1998; **47**· 409–413

8 Haupt W, Stofft E. Elasticity and tensile strength of human dural matter. *Verhandl Anat Gesellsch* 1978, **72**: 139–44

9 Meiklejohn BH. The effect of rotation of an epidural needle *Anaesthesia* 1987; **42**: 1180–2

10 Eisenstein S. Measurement of the lumbar canal in two racial groups. *Clin Orthop* 1976; **115**: 42

11 Holloway TE, Telford RJ. Observations on deliberate dural puncture with a Tuohy needle: depth measurements. *Anaesthesia* 1991; **46**: 722–4

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Altered globe dimensions of axial myopia as risk factors for penetrating ocular injury during peribulbar anaesthesia

S. B. Vohra[1]* and P. A. Good[2]

[1]*Department of Anaesthesia and* [2]*Birmingham and Midland Eye Centre, City Hospital NHS Trust, Dudley Road, Birmingham, UK*

**Corresponding author*

We measured the range of equatorial horizontal widths (EHW) in axially myopic eyes and identified the sites of staphyloma using B scan echography. One hundred eyes in 50 patients were studied. The axial lengths (ALs) were sorted into five groups of increasing severity of myopia. The group mean AL, group mean EHW and the ratio of EHW/AL was calculated for each range. The results suggest that the increase in the AL in an axially myopic eye is associated with an increase in the EHW. However, this increase in the group mean EHW is relatively small (2.3 mm) compared with the increase mean AL (8.2 mm) across the entire range. The ratio of EHW/AL decreased with an increase in the group mean AL. Therefore, the increase in EHW in an axially myopic eye is unlikely to be a significant risk factor for inadvertent ocular injury for peribulbar injections if a careful single medial canthal approach is used. There was high incidence of staphylomas in eyes with AL >29 mm, most were inferior to the posterior pole of the globe, and there were none at the equator.

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Keywords: myopia; axial length; equatorial horizontal width; staphyloma; globe penetration

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Regional anaesthesia of the eye is a safe and reliable technique for various types of ocular surgery. However, complications include the sight-threatening inadvertent needlestick injuries of the globe. There are a number of risk factors that predispose to needle penetration during retrobulbar and traditional peribulbar injections, including axial myopia. The risk of perforation is said to be 30 times greater in eyes with an axial length (AL) of 26 mm or greater compared with eyes with normal AL (23 mm or less).[1]

Recently, there has been an increase in the use of peribulbar blocks using the single medial canthal approach for various types of ocular surgery. In patients with axial myopia, the AL of the globe increases and the equatorial horizontal width (EHW) is expected to increase with it. Theoretically, this increase in the width of the globe in these eyes could be perceived to be a risk factor for an inadvertent ocular injury with the medial canthal approach. However, to date, there have been no studies addressing this issue. We looked into the relationship between the AL and EHW of the axially myopic eyes in order to identify the risk of perforation with the changing width of the globe. The incidence as well as the site of staphyloma in the axially myopic eyes was also investigated.

Patients and methods

ALs and EHWs of 100 axially myopic yes (AL >23 mm) in 50 patients presenting for cataract surgery were measured. The patients were recruited consecutively for each group of myopia of increasing severity: borderline myopia (AL: 23–25 mm); mild myopia (25.1–27 mm); moderate myopia (27.1–29 mm); high myopia (29.1–31 mm); and very high myopia (>31 mm). Each group had 10 patients (20 eyes). There were 26 females and 24 males with an age range of 52–85 yr (mean 70.3 yr). None of the patients had undergone any form of ocular surgery previously and their eyes were healthy other than lens opacification.

ALs were measured using a Canon KU1™ biometry apparatus and checked using an Alcon Digital B 2000™ B scanner to ensure that the measurements were to the macula. EHW was measured from the temporal to nasal equator using the B scanner. The scans were recorded through closed lids holding the scanning probe in the horizontal position. None of the B scan measurements was made through the lens. This was done to avoid distortion of the globe produced as a result of higher speed of transmission of sound waves through the lens compared with other ocular media. Three measurements

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of AL and EHW were made from each eye and mean values obtained for each. The presence or absence of staphyloma and its location were also noted during B scan echography.

The correlation coefficient of the AL and EHW measurements was calculated and analysis of covariance used to represent the relationship between them.

Results

The correlation coefficient between the measurements of the AL (n=100) and EHW (n=100) obtained from 50 patients was 0.80 (P<0.001, Fig. 1).

By apportioning the total variation in EHW between subjects, the within-subject association with length and unexplained or residual variation, a relationship of the following form was produced:

$$\text{EHW}=a\cdot\text{constant}+\text{between-subject variation}+b\cdot\text{AL}+\text{residual}$$

where b is the slope of the line that best describes how EHW changes with AL within an individual. The regression coefficient b was 0.281, that is, for each increase of 1 mm in AL within an individual, the EHW is predicted to increase by 0.281 mm. The within-subject correlation, which reflects how well the pairwise points all conform to a line with the same slope, was 0.93.

Similar results were obtained when a log EHW–log AL relation was explored (r=0.81). The coefficient of the slope was 0.32 (t-value=18.5).

Table 1 shows the grouped mean values including AL, EHW and the ratio of the group mean EHW *versus* group mean AL for each range of AL. The group mean AL increased by 8.2 mm, the group mean EHW increased by only 2.3 mm across the full range of axial lengths studied. The ratio EHW/AL decreased with the increasing severity of axial myopia (Fig. 2).

There were no staphylomas in the eyes of AL <27 mm, whereas 22 out of 60 eyes (37%) with AL >27 mm revealed the presence of a staphyloma. This incidence increased to 60% in the group with AL >31 mm (Table 2).

Eighteen (82%) staphylomas were located inferior to the posterior pole, whereas four (18%) were at the posterior pole of the globe. No staphylomas were found at the equator. Twelve (54.5%) of the staphylomas were unilateral, three in the 27.1–29 mm group, five in the 29.1–31 mm group, and four in the group with AL >31 mm.

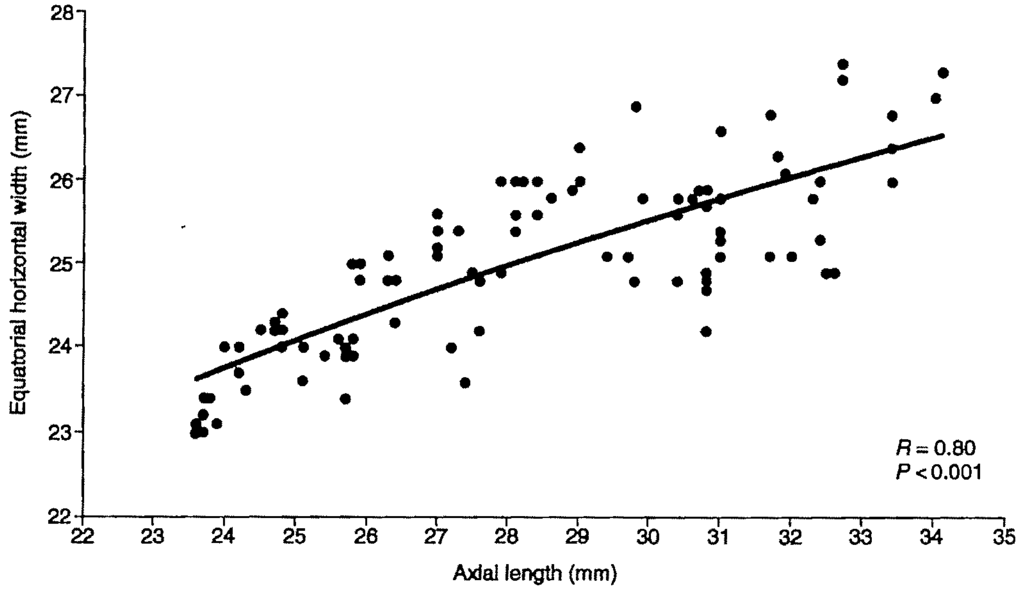

Fig 1 Relationship between AL and EHW of 100 axially myopic eyes.

Table 1 Grouped data–mean AL, mean EHW and mean ratio EHW/AL

Group	AL (mm) (number of eyes)	Mean AL (mm) (SD)	Mean EHW (mm) (SD)	Mean ratio EHW/AL (SD)
1	23–25 (20)	24.2 (0.45)	23.7 (0.47)	0.98 (0.01)
2	25.1–27 (20)	26.0 (0.60)	24.4 (0.60)	0.94 (0.01)
3	27.1–29 (20)	28.1 (0.62)	25.4 (0.76)	0.91 (0.02)
4	29.1–31 (20)	30.5 (0.50)	25.5 (0.67)	0.83 (0.03)
5	>31 (20)	32.4 (0.88)	26.0 (0.84)	0.79 (0.02)

Discussion

Local anaesthetic blocks are widely used for eye surgery. The first description of the retrobulbar block using cocaine was published by Herman Knapp in 1884.[2] Whilst retrobulbar blocks have been in use for over a century, peribulbar blocks have developed since the 1970s.[3] In the traditional retrobulbar block, the local anaesthetic is deposited in the posterior intraconal space using an inferotemporal route.[4 5] During the traditional peribulbar block, injections are made around the mid or retrobulbar but essentially in the periconal space of the globe. Two injections are usually performed, one inferior and another superior to the globe.[6] Complications resulting from local anaesthesia for the eye are relatively few. However, loss of vision as a consequence of the inadvertent puncture of the globe is obviously a dire outcome of what is considered to be a simple procedure. The puncture can result in vitreoretinal and choroidal haemorrhage, retinal detachment and delayed proliferative vitreoretinopathy. Foveal injury, optic nerve trauma and endophthalmitis have also been reported.[1]

The incidence of perforation during local anaesthesia for various types of eye surgery was reported to be 0.1% in 1965[7] and 0.075% in 1978.[8] The incidence of perforation during peribulbar anaesthesia in patients presenting for cataract surgery has been quoted to be 0.024%.[9] There are various factors that predispose to the inadvertent puncture of the globe during local anaesthesia. Axial myopia and anatomical abnormalities resulting from previous scleral buckling procedures are well known hazards.[7 8 10] The presence of a staphyloma, enophthalmos, multiple injections, faulty technique, uncooperative patient and the type of needle used are also important.[1]

Patients presenting with axial myopia have a 30 times greater risk of globe puncture compared with those patients with normal AL. A risk rate of one perforation for every 140 peribulbar blocks in eyes with AL >26 mm has been calculated.[1] The inferotemporal quadrant of the globe, followed by disc and macula, is the commonest reported site of perforation following retrobulbar and the traditional double peribulbar blocks. This is not surprising as the majority of blocks are performed using an inferotemporal route. Perforation has also been reported in the nasal quadrant.[11] Attempts have been made to reduce the incidence of ocular injury by using blunt or curved needles. However, contrary to the expectation and the view expressed by Lichter,[12] the incidence of needle penetration is not lowered with the use of these needles.[13 14]

The single medial canthal approach for peribulbar anaesthesia is a promising technique for ocular surgery. The injection is made using a 25G, 16-mm or 25-mm-long needle at the medial canthus with the eye fixed in the primary gaze. The path of the needle is essentially

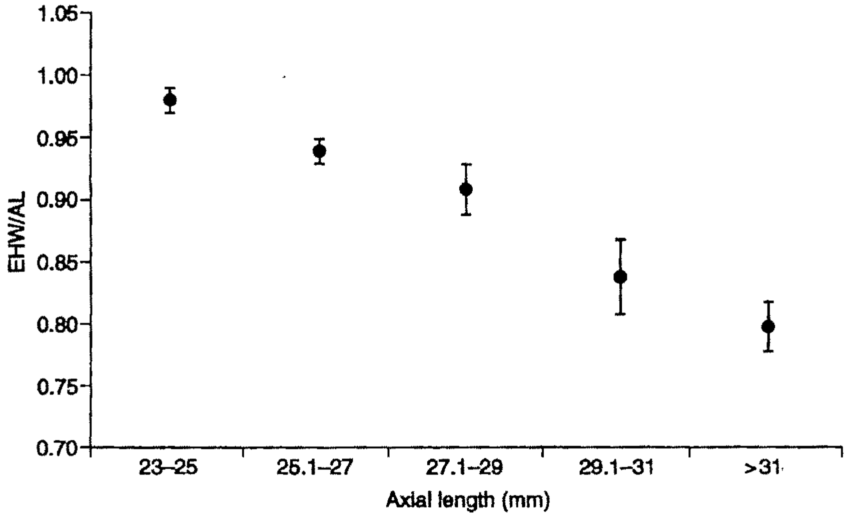

Fig 2 The relationship between EHW/AL and the group mean of ALs.

Table 2 Incidence of staphyloma with increasing myopia

Group	AL (mm)	Number of eyes	Number of staphylomas
1	23–25	20	0
2	25 1–27	20	0
3	27 1–29	20	3 (15%)
4	29.1–31	20	7 (35%)
5	>31	20	12 (60%)

perpendicular to the coronal plane along the medial wall of the orbit. The local anaesthetic is injected beyond the equator of the globe, around the posterior pole, in the peribulbar, extraconal space. The injection provides a high quality of analgesia and akinesia of the globe as well as lids especially, with a large volume of local anaesthetic. This is due to episceral, that is, a subtenon spread of local anaesthetic.[15]

It is a well-established fact that AL, particularly in axial myopes, is a risk factor for globe injury during the inferotemporal approach. However, the literature has not addressed the issue of the relationship between the EHW and AL in axial myopia. More importantly, what has not been investigated is whether the change in EHW is large enough to be a risk factor during the single medial canthal approach. Our results would suggest that there is an increase in the EHW associated with the increase in AL in the axially myopic eyes. However, the increase in the EHW is a modest one. It is clear from the analysis of the grouped data for AL and EHW in Table 1, that the increase in the group mean EHW width of 2.3 mm across the full range of ALs studied is significantly lower than the increase in the group mean AL of 8.2 mm. Expressed differently, there is a decrease in the ratio EHW/AL with increasing severity of axial myopia. It is obvious that the shape of the eye would tend to become increasingly ellipsoid rather than globular in the patients with increasing axial myopia.

Therefore, the increase in EHW in an axially myopic eye is possibly not a significant risk factor for inadvertent ocular injury during peribulbar injections where a careful single medial canthal approach is used, provided the eye is fixed in the primary gaze during the injection. However, it is conceivable that poor technique, angulation of the needle tip towards the globe, poor patient cooperation, movements of the head or eye, especially abduction, may cause problems.

Staphyloma is an outpouching of the globe resulting from the pathological thinning of sclera, choroid and retina. It is a fairly common finding in axially myopic eyes. However, previous studies have not established the relationship between the incidence or location of staphylomas and the severity of myopia.[16] It is noteworthy that there were no staphylomas in the eyes with AL <27 mm (mild myopia) in our study. The numbers increased dramatically from 15% in group 3 (moderate myopia) to 60% in group 5 (very high myopia) presenting with AL >31 mm. The site of the staphyloma in relation to the site of injection is of obvious importance. The majority of the staphylomas in our study were found to be inferior to the posterior pole of the globe. There is a high incidence of perforations in the inferotemporal quadrant of the globe even in the eyes with normal AL. Therefore, it is not difficult to conceive that the axially myopic eye is at risk, not only due to its increased AL, but also to the presence of an inferior or posterior staphyloma. It would be prudent to avoid the use of inferotemporal route in these eyes. It is interesting to note that there were no staphylomas in the nasal equatorial region in the eyes studied. Thus, the medial canthal approach, theoretically, may be less hazardous in axial myopes. Of course, the relative ratio of globe and orbital volumes, the extent of the space available between the medial aspect of the globe and the medial wall of the orbit are the factors that also have to be considered. Whilst biometry gives an indication of AL during routine assessment of the cataract patients, B scan echography is needed to locate the site and size of the globe wall abnormalities.

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References

1. Duker JS, Belmont JB, Benson WE, *et al.* Inadvertent globe perforation during retrobulbar and peribulbar anesthesia. *Ophthalmology* 1991; **98**: 519–26
2. Altman AJ, Albert DM, Fournier GA. Cocaine's use in ophthalmology: our 100 year heritage *Surv Ophthalmol* 1985; **29**: 300–6
3. Davis DB, Mandel MR Posterior peribulbar anesthesia. an alternative to retrobulbar anesthesia. *J Cataract Refract Surg* 1986; **12**: 182–4
4. Atkinson WS Retrobulbar injection of anesthetic within the muscular cone (cone injection). *Arch Ophthalmol* 1936; **16**: 494–503
5. Unsöld R, Stanley JA, DeGroot J. The CT-topography of retrobulbar anesthesia· anatomic-clinical correlation of complications and suggestion of a modified technique *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 1981, **217**: 125–36
6. Hamilton RC. Techniques of orbital regional anaesthesia. *Br J Anaesth* 1995; **75**: 88–92
7. Cbis PA. General discussion: opening remarks In: Schepens CL, Regan CDJ, eds. *Controversial Aspects of the Management of Retinal Detachment.* Boston: Little, Brown, 1965; 222
8. Ramsay RC, Knobloch WH. Ocular perforation following retrobulbar anesthesia for retinal detachment surgery. *Am J Ophthalmol* 1978; **86**: 61–4
9. Kimble JA, Morris RE, Witherspoon CD, Feist RM. Globe perforation from peribulbar injection. *Arch Ophthalmol* 1987, **105**; 749
10. Rosen DA. Anesthesia in ophthalmology. *Can Anesth Soc J* 1962, **9**: 545–9
11. McCombe M, Heriot W. Penetrating ocular injury following local anaesthesia. *Aust NZ J Ophthalmol* 1995; **23**· 33–6
12. Lichter PR. Avoiding complications from local anesthesia (editorial). *Ophthalmology* 1998; **95**: 565–6
13. Hay A, Flynn HW, Hoffman JI, Rivera AH. Needle penetration of the globe during retrobulbar and peribulbar injections. *Ophthalmology* 1991, **98**: 1017–24
14. Grizzard WS, Kirk NM, Pavan PR, Antworth MV, Hammer ME, Roseman RL. Perforating ocular injuries caused by anaesthesia personnel. *Ophthalmology* 1991; **98**: 1011–6
15. Ripart J, Prat-Pradal D, Vivien B, Charavel P, Eldjam JJ. Medial canthus episcleral (sub-Tenon) anesthesia imaging *Clin Anat* 1998, **11**: 390–5
16. Hoffman JD, Heath DA. Staphyloma and other risk factors in axial myopia. *J Am Optom Assoc* 1987; **58**: 907–13

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Onset/offset characteristics and intubating conditions of rapacuronium: a comparison with rocuronium

T. J. Zhou, P. F. White*, J. W. Chiu, G. P. Joshi, K. K. Dullye, L. L. Duffy and W. K. Tongier

Department of Anaesthesiology and Pain Management, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75235, USA

**Corresponding author*

We compared onset and offset of action and tracheal intubating conditions after rapacuronium and rocuronium in 60 patients in a randomized, assessor-blinded study. Following induction of anaesthesia with propofol 2.5 mg kg^{-1}, either rapacuronium 1.5 mg kg^{-1} (n=30) or rocuronium 0.6 mg kg^{-1} (n=30) was administered to facilitate tracheal intubation. Anaesthesia was maintained with either a propofol infusion (100 µg kg^{-1} min^{-1}) or sevoflurane (1% end-tidal) with 66% nitrous oxide (N_2O), n=15 in each subgroup. Neuromuscular monitoring was performed using an electromyographic (EMG) device (Datex Relaxograph). The lag times (mean 42 (SD 11) s and 44 (16) s), maximum block (99 (2)% and 98 (3)%) and intubating conditions at 60 s (good-to-excellent in 86% and 84% of patients) were similar for rapacuronium and rocuronium, respectively. The onset time of rapacuronium was shorter than rocuronium (87 (20) *vs* 141 (65) s, P<0.001), and the degree of block at 60 s was greater (69 (26) *vs* 50 (27)%, P<0.05). Twenty-five per cent recovery was shorter with rapacuronium than rocuronium during propofol (15.0 (3.2) *vs* 39.1 (14.2) min, P<0.001) and sevoflurane (15.1 (4.2) *vs* 47.8 (19.0) min, P<0.001) anaesthesia. We conclude that rapacuronium 1.5 mg kg^{-1} had a more rapid onset, similar intubating conditions, and shorter recovery times than rocuronium 0.6 mg kg^{-1}.

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Rapacuronium (ORG 9487), the 16-*N*-allyl, 17-β-propionate analogue of vecuronium, is a new aminosteroidal non-depolarizing neuromuscular blocking agent with a rapid onset and short duration of action.[1–4] It is less potent than rocuronium, requiring a minimum effective dose to produce 90% paralysis (ED_{90}) of 1.15 mg kg^{-1} compared to an ED_{95} of 0.3 mg kg^{-1} for rocuronium.[2 5] As a result, rapacuronium would be expected to have a more rapid onset and better intubating conditions at 60 s than other currently available non-depolarizing neuromuscular blocking drugs. Because the effect of neuromuscular blocking drugs is known to be influenced by the anaesthetic technique, the effect of the maintenance anaesthetic (volatile *versus* intravenous) on the recovery profile after rapacuronium-induced blockade must be examined.

This study was designed to test the hypothesis that standard intubating doses of rapacuronium and rocuronium differ with regard to their onset/offset of action and tracheal intubating conditions. In addition, we compared the initial recovery profiles of the two non-depolarizing neuromuscular blocking drugs during propofol- or sevoflurane-based anaesthesia.

Patients and methods

After obtaining institutional review board approval and written, informed consent, 60 ASA I-II patients aged 21–75 yr undergoing minor orthopaedic surgical procedures were enrolled in the study. Patients with hepatic, renal or neuromuscular disease, or those taking anticonvulsants, aminoglycoside or polypeptide antibiotics, or any other medication known to modify the action of neuromuscular blockers, were excluded from the study. Exclusion criteria also included body weight >130% of ideal and anticipated difficulty in performing tracheal intubation.

On arrival in the operating room, the electrocardiogram (ECG), haemoglobin oxygen saturation (Sp_{O_2}), and non-invasive arterial pressure were monitored. After premedica-

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Table 1 Tracheal intubating conditions according to a three-point scale developed at the Copenhagen Consensus Conference[6]

Variables	**Clinically acceptable**		**Clinically unacceptable**
	Excellent	**Good**	**Poor**
Position of vocal cords	Abducted	Intermediate	Closed
Movement of vocal cords	None	Moving	Closing
Ease of laryngoscopy	Easy	Fair	Difficult
Airway reaction	None	Diaphragm	Sustained (>10 s)
Movement of the limbs	None	Slight	Vigorous

tion with midazolam 2 mg i.v., anaesthesia was induced with propofol 2.5 mg kg^{-1} and fentanyl 1.5 µg kg^{-1} i.v., followed 2 min later by either rapacuronium 1.5 mg kg^{-1} (n=30) or rocuronium 0.6 mg kg^{-1} (n=30) according to a computer-generated randomization sequence. One minute after administration of the neuromuscular blocking drug, direct laryngoscopy was initiated followed by tracheal intubation. Intubating conditions were assessed using a three-point scale (Table 1)[6] by an experienced anaesthetist who was blinded to which neuromuscular blocking drug was administered. A 20-s interval was allowed for the first attempt at intubation, and in the event of failure, a second attempt was made at 90 s.

Anaesthesia was initially maintained with either a propofol infusion 100 µg kg^{-1} min^{-1} or 1% sevoflurane (end-tidal) according to random assignment, in combination with 66% nitrous oxide (N_2O) in oxygen using a semiclosed circuit with a total flow of 3 litres min^{-1} (n=15 in each subgroup). Incremental bolus doses of fentanyl were administered as required. Ventilation was controlled to maintain an end-tidal partial pressure of carbon dioxide ($P_{ET_{CO_2}}$) between 4.3 and 5.5 kPa. A skin thermistor was taped to the hand close to the electromyographic (EMG) monitoring site. Skin temperature and central temperature (measured at the oesophagus) were maintained above 32.5°C and 36.5°C, respectively, using warmed blankets. End-expired partial pressures of carbon dioxide, nitrous oxide and sevoflurane were measured using a multiple gas analyser (Capnomac Ultima; Datex) which had been calibrated using a standard gas mixture (Quick Cal, Datex).

Neuromuscular monitoring was performed using the Datex Relaxograph (Helsinki, Finland) to record the EMG response of the adductor pollicis to supramaximal square-wave train-of-four (TOF) stimulation of the ulnar nerve at the wrist for 0.2 ms every 10 s during the onset period, and every 20 s following tracheal intubation. The EMG recording apparatus was connected to the patient before induction of anaesthesia, and the 'baseline' calibration sequence (which required 45–60 s to complete) performed as soon as the patient lost consciousness. This was followed 1 min later by a bolus dose of either rapacuronium or rocuronium, administered over 5 s into a rapidly flowing i.v. infusion line positioned in the contralateral forearm from that used for neuromuscular monitoring. Neuromuscular blockade was allowed to recover spontaneously until the first response to TOF stimulation (T_1) achieved at least 25% of the baseline value.

Clinically significant cardiovascular events (i.e. changes in arterial pressure or heart rate 30% above or below baseline values) occurring within 10 min of administration of the study drug and any possible histamine release-related signs (e.g. flushing, cutaneous erythema, bronchospasm) were recorded. An adverse event was defined as an unusual or unexpected clinical sign, which manifested itself or worsened during the intraoperative study period, irrespective of whether it was thought to be study drug related.

The following parameters were measured or calculated from the EMG recordings: (i) the time from the end of study drug injection until first depression T_1 (lag time); (ii) the time from the end of study drug injection until 95% depression T_1 (onset time); (iii) the degree of block at 60 s; (iv) the extent of maximum block; and (v) the time from the end of study drug injection until spontaneous recovery of T_1/T_0 to 25%. The time to 25% recovery T_1/T_0 was calculated by using the final EMG T_1/T_0 value as a reference.[7]

The sample size was determined by performing an *a priori* power analysis to detect a difference of 30% or more in the onset time between the two neuromuscular blocking drugs (0.05 two-sided significance level, 80% power) based on previously published data.[1 5] Analysis of variance (ANOVA) was used for analysing physical characteristics, and Fisher's exact test was utilized for assessing intubating conditions and adverse effects. Student's t-test or Mann–Whitney U-test was used for analysing onset and offset times between the two neuromuscular blocking drugs and the two anaesthetic techniques as appropriate. Differences between groups were considered statistically significant when the P-value was <0.05.

Results

The four subgroups were comparable with regard to age, weight, height, sex, ASA class and maintenance anaesthetic requirement (Table 2).

The lag times were similar after the two drugs but the onset time of rapacuronium was significantly shorter than that of rocuronium (Table 3). The degree of block at 60 s produced by rapacuronium was also greater than rocuronium (Table 3). Tracheal intubating conditions were comparable for both neuromuscular blocking drugs, with a

Table 2 Physical characteristics and anaesthetic drug requirements for the four study subgroups. Values are mean (SD or range), or numbers. No significant differences were noted between the four groups for any variable

	Rapacuronium		**Rocuronium**	
	Propofol (*n*=15)	**Sevoflurane (*n*=15)**	**Propofol (*n*=15)**	**Sevoflurane (*n*=15)**
Age (yr)	36 (21–70)	38 (21–63)	42 (29–68)	40 (22–75)
Weight (kg)	76 (15)	77 (16)	79 (11)	77 (18)
Height (cm)	170 (9)	171 (11)	173 (13)	165 (13)
Sex (M/F)	9/6	8/7	9/6	8/7
ASA (1/2)	5/10	7/8	6/9	5/10
Propofol (μg kg^{-1} min^{-1})	108 (20)	—	105 (21)	—
Sevoflurane (end-tidal %)	—	1.1 (0.1)	—	1.1 (0.1)

Table 3 Onset and initial recovery variables as well as intubating conditions after rapacuronium 1.5 mg kg^{-1} or rocuronium 0.6 mg kg^{-1}. Propofol + sevoflurane represents pooled data of the two subgroups. Values are mean (SD (median)), or numbers (percentages). $^*P<0.05$, $^{**}P<0.001$ *vs* rocuronium

	Rapacuronium	**Rocuronium**
Lag time (s)	42 (11 (40))	44 (16 (45))
Onset time (s)	87 (20 (81))**	141 (65 (125))
Block at 60 s (%)	69 (26 (82))*	50 (27 (55))
Maximum block (%)	99 (2 (100))	98 (3 (100))
Intubating conditions at 60 s (*n*, %)		
Excellent	16 (53)	14 (47)
Good	10 (33)	11 (37)
Poor	1 (3)	2 (7)
Impossible	3 (10)	3 (10)
Time to recovery of T_1/T_0 to 25% (min)		
Propofol	15.0 (3.2 (14.3))**	39.1 (14.2 (43.3))
Sevoflurane	15.1 (4.2 (15.0))**	47.8 (19.0 (40.5))
Propofol + sevoflurane	15.1 (3.7 (14.5))**	43.4 (16.8 (41.1))

good-to-excellent rating achieved in 87% and 83% of patients at 60 s with rapacuronium and rocuronium, respectively (Table 3). Intubation was not possible in three (10%) patients in each group at 60 s due to inadequate muscle relaxation; however, they were successfully intubated at 90 s with an equal distribution of excellent, good and poor scores among the three patients in each group. Recovery of T_1/T_0 to 25% was similar for each neuromuscular blocking drug during propofol- or sevoflurane-based anaesthesia (Table 3). When compared with rocuronium, recovery of T_1/T_0 to 25% after rapacuronium was significantly shorter during both propofol- and sevoflurane-based anaesthesia (Table 3).

Adverse events were noted in five patients after rapacuronium and four patients after rocuronium. In the rapacuronium group, one case of severe bronchospasm was noted after tracheal intubation in a 35-yr-old male smoker. The other adverse events (e.g. transient tachycardia or hypotension) occurred after tracheal intubation and administration of the maintenance anaesthetic. They required no treatment and were considered unlikely to be related to the study drugs.

Discussion

This study confirmed the rapid onset of neuromuscular block after rapacuronium 1.5 mg kg^{-1} i.v.[3 4] The lag time and extent of maximum block determined in our study were in agreement with those reported by van den Broek and colleagues (42 (11) *vs* 41 (13) s and 99 (2) *vs* 99 (1)%, respectively),[3] whereas the onset time and blockade at 60 s were similar to the findings of Debaene and colleagues (87 (20) *vs* 96 (20) s and 69 (26) *vs* 62 (31)%, respectively).[4]

The dose–response relationship for rapacuronium has not been well established. In their preliminary investigation, Wierda and colleagues[2] reported an ED_{90} of 1.15 mg kg^{-1} for rapacuronium. However, the dosage used was based on the bromide salt of rapacuronium, whereas the dosage calculation in the more recent studies was based on the free base (100 mg=113.4 mg of the bromide salt). Thus, a dose of rapacuronium 1.5 mg kg^{-1} in our study would represent $1.5 \times ED_{90}$ (recalculated for the free base). Our study demonstrated that even at this lower dose ($1.5 \times ED_{90}$ *vs* $2 \times ED_{90}$), the onset of action was more rapid and the degree of blockade at 60 s greater with rapacuronium compared to rocuronium.

This finding is consistent with the inverse relationship between potency of non-depolarizing neuromuscular blocking drugs and the speed of onset of effect.[8] With less potent drugs like rapacuronium, more drug molecules are administered, thereby increasing the concentration gradient between the plasma and the motor end-plate.[9 10] An alternative explanation for the rapid onset of rapacuronium relates to its rapid equilibration between the plasma and effect sites.[11] The equilibration rate constant (*Keo*) of rapacuronium (0.41 min^{-1}) is more than twice that of rocuronium (0.17 min^{-1})[12] and 3.4 times that of vecuronium (0.12 min^{-1}).[13] Additionally, in animal studies rapacuronium has been shown to possess calcium channel blocking effects that produce vasodilatation 25–50 times greater than vecuronium.[14] Increased blood flow to skeletal muscle may also contribute to the rapid onset of neuromuscular blockade with rapacuronium.

The fast onset of neuromuscular blocking effect after rapacuronium coincides with the achievement of clinically acceptable (good-to-excellent) intubating conditions in the majority of patients at 60 s. Kahwaji and colleagues[15] reported good-to-excellent intubating conditions in 86% of young adults and 84% of elderly patients within 90 s after rapacuronium 1.5 mg kg^{-1}. However, our findings differed from those of Wierda and colleagues[1] who reported good-to-excellent intubating conditions at 60 s in 100% of patients. A possible explanation for this difference relates to the fact that tracheal intubation was performed 5–10 min after inhalation of isoflurane (1.0%) in combination with nitrous oxide in the earlier study. The onset time of rapacuronium 1.5 mg kg^{-1} in the laryngeal adductor muscles is 1.0 (0.2) min,[4] shorter than rocuronium 0.5 mg kg^{-1} at 1.4 (0.3) min[16] and approaching succinylcholine 0.5 mg kg^{-1} at 0.9 (0.1) min.[17] At the time of intubation, rapacuronium-induced neuromuscular block at the larynx would be nearly maximum, thereby facilitating tracheal intubation.

The 25% recovery time of rapacuronium was found to be longer in the present investigation compared to two previous studies by Wierda and colleagues.[1 2] These investigators reported that 25% T_1/T_0 recovery of rapacuronium was 8.0 (1.9) min and 8.9 (2.0) min during 1.0% isoflurane[1] and 1.0% halothane[2] anaesthesia, respectively. However, our results are consistent with those of Kahwaji and colleagues (14 (6) min for young adults and 17 (5) min for elderly adults) [15] and Purdy and colleagues (16.2 (4.0 min)).[18] The discrepancies are probably accounted for by the different drug moieties. A dose of 1.5 mg kg^{-1} in the present study is equivalent to 1.7 mg kg^{-1} in Wierda's studies, at least partially explaining the difference in 25% T_1/T_0 recovery time. Recovery time of T_1/T_0 to 25% after rapacuronium during either propofol- or sevoflurane-based anaesthesia was found to be significantly shorter than after rocuronium. The more rapid plasma clearance of rapacuronium contributes to its shorter duration of action (7.3 ml kg^{-1} min^{-1} *vs* 4.0 ml kg^{-1} min^{-1} for rocuronium).[19]

Recovery of T_1/T_0 to 25% with both neuromuscular blocking drugs was similar during propofol and sevoflurane anaesthesia. This finding may be related to the time-dependent potentiating effects of potent inhaled agents on non-depolarizing neuromuscular blocking drugs.[20] Although data for sevoflurane are not available, full isoflurane-induced potentiation of muscle relaxant activity requires 30–45 min of steady-state anaesthesia.[21] It is possible that the 25% recovery of T_1/T_0 after both rapacuronium and rocuronium would have been prolonged during sevoflurane (*vs* propofol) anaesthesia had the exposure occurred over a longer time interval. Xue and colleagues[22] have reported that recovery of T_1/T_0 to 25% after rocuronium 0.4 mg kg^{-1} was longer during sevoflurane anaesthesia (1.75%) compared to a propofol-based technique. However, in their study the patients received the volatile anaesthetic for ~40 min before the neuromuscular blocking drug was administered. The experimental design used by these investigators bears little relevance to the usual clinical situation; we therefore allowed for a much shorter stabilization period of ~1 min.

A shortcoming of the current study lies in the use of the Datex Relaxograph for monitoring neuromuscular function. As a result of the downward drift of the EMG amplitude over time, it is not uncommon for T_1/T_0 to regain only 70–80% of its baseline value despite a TOF ratio exceeding 0.9.[23] In the present study, the final T_1/T_0 values recovered to 81 (SD 9)% of baseline values, corresponding to TOF ratios of ⩾0.85. To compensate for this phenomenon, the values for 25% T_1/T_0 recovery times were determined by using proportional recalculation based on the final EMG T_1/T_0 value.[7]

In conclusion, rapacuronium 1.5 mg kg^{-1} exhibited a more rapid onset of action than rocuronium 0.6 mg kg^{-1} and provided good-to-excellent intubating conditions in the majority of patients at 60 s. The initial recovery time of rapacuronium was ~50% shorter than that of rocuronium, and was not significantly altered by the maintenance anaesthetic. These data suggest that rapacuronium is a useful addition to the armamentarium of currently available non-depolarizing neuromuscular blocking drugs for facilitating tracheal intubation in patients undergoing short surgical procedures.

Acknowledgement

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References

1 Wierda JM, van den Broek L, Proost JH, Verbaan BW, Hennis PJ. Time course of action and endotracheal intubating conditions of Org 9487, a new short-acting steroidal muscle relaxant: a comparison with succinylcholine. *Anesth Analg* 1993; **77** 579–84

2 Wierda JM, Beaufort AM, Kleef UW, Smeulers NJ, Agoston S. Preliminary investigations of the clinical pharmacology of three short-acting non-depolarizing neuromuscular blocking agents, Org 9453, Org 9489 and Org 9487. *Can J Anaesth* 1994; **41** 213–20

3 van den Broek L, Wierda JM, Smeulers NJ, Proost JH. Pharmacodynamics and pharmacokinetics of an infusion of Org 9487, a new short-acting steroidal neuromuscular blocking agent *Br J Anaesth* 1994; **73**: 331–5

4 Debaene B, Lieutaud T, Billard V, Meistelman C. ORG 9487 neuromuscular block at the adductor pollicis and the laryngeal adductor muscles in humans. *Anesthesiology* 1997; **86**: 1300–5

5 Kopman AF, Klewicka MM, Kopman DJ, Neuman GG. Molar potency is predictive of the speed of onset of neuromuscular block for agents of intermediate, short, and ultrashort duration. *Anesthesiology* 1999; **90**: 425–31

6 Viby-Mogensen J, Engbaek J, Eriksson LI, *et al.* Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. *Acta Anaesthesiol Scand* 1996; **40**: 59–74

7 Meretoja OA, Theroux M Can final EMG baseline be used as a reference to calculate neuromuscular recovery. *Acta Anaesthesiol Scand* 1997; **41**: 492–6

8 Bowman WC, Rodger IW, Houston J, Marshall RJ, McIndewar I. Structure: action relationships among some desacetoxy analogues of pancuronium and vecuronium in the anesthetized cat. *Anesthesiology* 1988; **69**: 57–62

9 Min JC, Bekavac I, Glavinovic MI, Donati F, Bevan DR. Iontophoretic study of speed of action of various muscle relaxants. *Anesthesiology* 1992; **77**: 351–6

10 Kopman AF. Gallamine, pancuronium and d-tubocurarine compared: is onset time related to drug potency? *Anesthesiology* 1989; **70**: 915–20

11 Wright P, Brown R, Lau M, Fisher DM. A pharmacodynamic explanation for the rapid onset/offset of rapacuronium bromide. *Anesthesiology* 1999; **90**: 16–23

12 Plaud B, Proost JH, Wierda JM, Barre J, Debaene B, Meistelman C. Pharmacokinetics and pharmacodynamics of rocuronium at the vocal cords and the adductor pollicis in humans. *Clin Pharmacol Ther* 1995; **58**: 185–91

13 Fisher DM, Wright PM. Are plasma concentration values necessary for pharmacodynamic modeling of muscle relaxants? *Anesthesiology* 1997; **86**: 567–75

14 Muir AW, Sleigh T, Marshall RJ, *et al.* Neuromuscular blocking and cardiovascular effects of Org 9487, a new short-acting aminosteroidal blocking agent, in anaesthetized animals and in isolated muscle preparations. *Eur J Anaesthesiol* 1998; **15**: 467–79

15 Kahwaji R, Bevan DR, Bikhazi G, *et al.* Dose-ranging study in younger adult and elderly patients of ORG 9487, a new, rapid onset, short-duration muscle relaxant. *Anesth Analg* 1997; **84**: 1011–8

16 Meistelman C, Plaud B, Donati F. Rocuronium (ORG 9426) neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis in humans. *Can J Anaesth* 1992; **39**: 665–9

17 Meistelman C, Plaud B, Donati F. Neuromuscular effects of succinylcholine on the vocal cords and adductor pollicis muscles. *Anesth Analg* 1991; **73**: 278–82

18 Purdy R, Bevan DR, Donati F, Lichtor JL. Early reversal of rapacuronium with neostigmine. *Anesthesiology* 1999; **91**: 51–7

19 Schiere S. Proost JH, Schuringa M, Wierda JM. Pharmacokinetics and pharmacokinetic-dynamic relationship between rapacuronium (Org 9487) and its 3-desacetyl metabolite (Org 9488). *Anesth Analg* 1999; **88**: 640–7

20 Withington DE, Donati F, Bevan DR, Varin F. Potentiation of atracurium neuromuscular blockade by enflurane: time-course of effect. *Anesth Analg* 1991; **72**: 469–73

21 Lambalk LM, de Wit APM, Wierda JM, Hennis PJ, Agoston S. Dose–response relationship and time course of action of Org 9426; a new muscle relaxant of intermediate duration evaluated under various anaesthetic techniques. *Anaesthesia* 1991; **46**: 907–11

22 Xue FS, Liao X, Tong SY, Liu JH, An G, Luo LK. Dose–response and time-course of the effect of rocuronium bromide during sevoflurane anaesthesia. *Anaesthesia* 1998; **53**: 25–30

23 Kopman AF, Justo MD, Mallhi MU, Abara CE, Neuman GG. The influence of changes in hand temperature on the indirectly evoked electromyogram of the first dorsal interosseous muscle. *Can J Anaesth* 1995; **42**: 1090–5

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Comparison of succinylcholine with two doses of rocuronium using a new method of monitoring neuromuscular block at the laryngeal muscles by surface laryngeal electromyography

T. M. Hemmerling[1]*, J. Schmidt[1], T. Wolf[1], P. Klein[2] and K. Jacobi[1]

Departments of [1]Anaesthesiology and [2]Surgery, University of Erlangen, Nuremberg, Germany
**Corresponding author: Postfach 1367, D-66363 St Ingbert, Germany*

We compared the onset of neuromuscular block with succinylcholine (1 mg kg^{-1}) and two doses of rocuronium (0.6 and 0.9 mg kg^{-1}) at the adductor pollicis muscle using electromyography (EMG) and acceleromyography (AMG), and at the adductor laryngeal muscles with a new electromyographic method using a disposable surface electrode attached to the cuff of a tracheal tube. At the larynx, the mean (±SD) time to 90% block and the onset time of succinylcholine (38±15 and 47±19 s, respectively) were significantly shorter ($P<0.01$) than for rocuronium 0.6 mg kg^{-1} (92±42 and 106±38 s) and rocuronium 0.9 mg kg^{-1} (52±31 and 64±30 s). We found that, with comparable degrees of neuromuscular block, the onset time of succinylcholine at the adductor pollicis was significantly shorter ($P<0.01$) than for rocuronium 0.6 mg kg^{-1} and 0.9 mg kg^{-1} (EMG, 80±39 *vs* 145±48 s and 99±31 s; AMG, 90±39 *vs* 124±53 s and 106±38 s). Clinical duration at the adductor pollicis (AMG) was significantly longer ($P<0.01$) for both rocuronium groups than for succinylcholine (T_4:T_1=0.7, 54±18 and 77±21 *vs* 8±6 min). The surface laryngeal electrode proved non-invasive, easy to use and reliable in measuring onset of the neuromuscular block at the larynx.

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Since its introduction in 1956, succinylcholine has been the main neuromuscular blocking drug for rapid-sequence induction (RSI) or difficult intubation.[1] Because of its potential to cause serious side effects, efforts have been undertaken to find an alternative non-depolarizing neuromuscular blocking drug with a short onset and offset of block to replace succinylcholine, especially for RSI.[2 3]

Rocuronium has been studied as an alternative to succinylcholine; in most studies, however, the onset and offset of the neuromuscular block have been measured at peripheral, easily accessible muscles. Neuromuscular blockade at the larynx should be compared with peripheral muscles, such as the adductor pollicis muscle, using similar monitoring methods, such as surface electromyography.

For more than two decades, intraoperative monitoring of the recurrent laryngeal nerve has been the focus of extensive research in otolaryngological surgery of the thyroid gland. Initially, needle electrodes were used, placed translaryngeally through the operating site;[4] later, needle electrodes were applied endoscopically.[5] Although electromyographic signals obtained via needle electrodes are regarded as the gold standard in monitoring, special expertise is required during insertion and electrodes are needed which are not displaced during surgery.[5]

Recently, non-invasive forms of monitoring the laryngeal response to stimulation of the recurrent laryngeal nerve have been tested. Special tracheal tubes with integrated electrodes proved reliable but expensive,[6] and a postcricoid electrode inserted into the upper pharynx lacked reliability.[6]

We used a new disposable surface electrode,[7] attached to a tracheal tube and placed between the vocal cords at intubation, to measure the onset of neuromuscular block obtained with two doses of rocuronium compared with succinylcholine.

Materials and methods

After approval of the local ethics committee and written informed consent had been obtained, 90 patients undergoing surgery of the thyroid gland were included in the study. Pregnant women, patients with neuromuscular, hepatic or renal disease, and patients receiving medication known to interact with neuromuscular blocking drugs were excluded.

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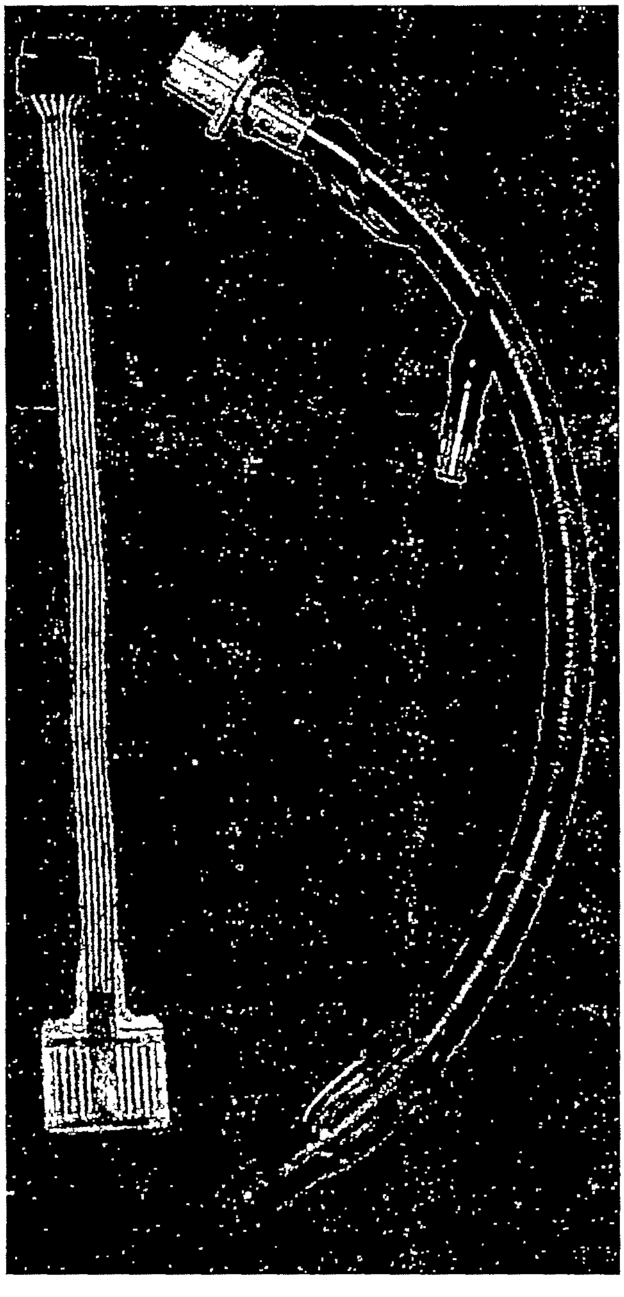

Fig 1 Disposable surface laryngeal electrode. The distal electrode part is glued around the tube 2 cm above the cuff and placed between the vocal cords at intubation; the electrode is proximally secured around the tube to avoid misplacement during surgery

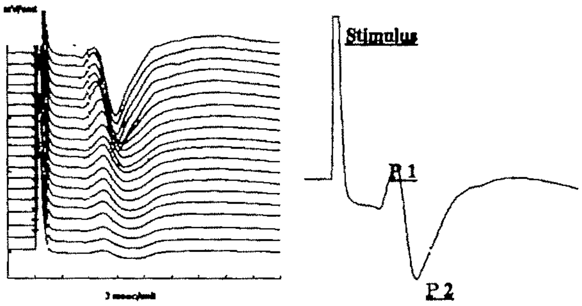

Fig 2 A compound action potential of the electromyographic response of the laryngeal muscles after injection of the neuromuscular blocking drug and decrease of the neuromuscular response. Amplitude height P1–P2 was measured as the neuromuscular response (mean (SD) (range)).

Anaesthesia was induced using an infusion of remifentanil 0.5 $\mu g\ kg^{-1}\ min^{-1}$. Two minutes later, target-controlled infusion of propofol (target concentration 4 $\mu g\ ml^{-1}$) was started, programmed to reach the target concentration within 30 s. After induction of anaesthesia, the patients were ventilated using a face mask for 3 min and intubated using an oral Woodbridge tube (Mallinckrodt, Bicester, UK) (size 7.0 for females and 8.0 for males) with the surface laryngeal electrode (Magstim company, Whitland, UK) attached 2 cm above the beginning of the cuff (Fig. 1). The electrode was placed between the vocal cords for optimal electromyography (EMG) recording. The recurrent laryngeal nerve function of all patients was checked 3 days after operation using indirect laryngoscopy by the otolaryngologist. Any lesion or damage to the vocal cords due to the surface laryngeal electrode was noted.

Anaesthesia was maintained by target-controlled infusion of propofol (target concentration 3 $\mu g\ ml^{-1}$) and remifentanil 0.25 $\mu g\ kg^{-1}\ min^{-1}$; mechanical ventilation (30% oxygen in air) was adjusted to achieve an end-tidal CO_2 pressure of 26–35 mm Hg.

After induction and fixation of the tracheal tube, the recurrent laryngeal nerve was stimulated transcutaneously with an external nerve stimulator (Multiliner®; Tönnies, Würzburg, Germany) at the notch of the thyroid cartilage, to produce maximum response of the adductor laryngeal muscles. The external nerve stimulator has a probe that is attached at the neck with an elastic band. It delivers a current between 0 and 70 mA. Single twitch stimuli (0.1 Hz; pulse width 0.2 ms) were applied to the left recurrent nerve to determine supramaximal stimulation, and were recorded using Multiliner® software. The current was increased to that with the maximal EMG response (<70 mA) and then increased by 10 mA to ensure supramaximal stimulation. The amplitude of the compound action potentials was measured and recorded (Fig. 2). After stimulation of the left ulnar nerve with Ag/AgCl electrodes, evoked EMG single-twitch responses (0.1 Hz; pulse width 0.2 ms) from the adductor pollicis muscle via Ag/AgCl electrodes placed over the base of the thenar area were recorded; automatic calibration of the Datex Relaxograph® NMT 100 (Datex Instrumentarium Corporation, Helsinki, Finland) was used to determine supramaximal stimulation (0–70 mA). The right thumb was equipped with an acceleromyographic (AMG) probe to record the neuromuscular response of the adductor pollicis muscle. The automatic calibration setup of the TOF-guard^{NMT} (Organon, Helsinki, Finland) was used to determine supramaximal stimulation (single twitch, 0.1 Hz).

After no change in the neuromuscular response had been detected at all three sites for at least 10 min, the patients

Table 1 Physical characteristics (mean (SD) (range))

Group	Age (yr)	Sex (M/F)	Height (cm)	Weight (kg)	ASA (1, 2, 3)
All groups	52 (15) (20–81)	29/61	168 (9) (145–190)	74 (15) (47–127)	27/45/18
Succinylcholine 1.0 mg kg^{-1}	55 (14) (20–77)	9/21	167 (9) (145–182)	71 (14) (49–98)	9,14,7
Rocuronium 0.6 mg kg^{-1}	50 (16) (26–81)	10/20	168 (8) (152–189)	77 (17) (47–127)	8,18,4
Rocuronium 0.9 mg kg^{-1}	51 (13) (29–78)	10/20	168 (10) (150–190)	74 (14) (49–100)	10,13,7

Table 2 Onset time and peak effect of neuromuscular block after succinylcholine 1 mg kg^{-1} and rocuronium 0.6 mg kg^{-1} or 0.9 mg kg^{-1} at the larynx and adductor pollicis muscle. Mean (SD) (range); *$P<0.01$, larynx *vs* adductor pollicis (EMG and AMG); †$P<0.01$, succinylcholine *vs* both doses of rocuronium, ‡$P<0.01$, rocuronium 0.9 mg kg^{-1} *vs* rocuronium 0.6 mg kg^{-1}

	Larynx (EMG)	Adductor pollicis (EMG)	Adductor pollicis (AMG)
Succinylcholine 1 mg kg^{-1} (n=30)			
Maximum block (%)	94 (11) (90–100)	94 (6) (76–100)	100 (100–100)
Lag time (s)	20 (11) (10–50)*	41 (14) (10–80)	43 (15) (5–90)
90% block T_1/T_0 (s)	38 (15) (10–60)*†	71 (39) (30–240)†	72 (26) (11–180)†
Onset time (s)	47 (19) (20–120)*†	80 (39) (40–260)†	90 (39) (21–220)†
Rocuronium 0.6 mg kg^{-1} (n=30)			
Maximum block (%)	95 (3) (90–100)	95 (5) (85–100)	100 (100–100)
Lag time (s)	22 (11) (10–50)*	48 (19) (30–80)	44 (21) (20–80)
90% block T_1/T_0 (s)	92 (42) (30–170)*	127 (48) (50–260)	117 (39) (30–200)
Onset time (s)	106 (38) (50–200)*	145 (48) (70–280)	124 (53) (40–280)
Rocuronium 0.9 mg kg^{-1} (n=30)			
Maximum block (%)	98 (5) (81–100)	93 (6) (78–100)	100 (100–100)
Lag time (s)	21 (13) (10–70)*	41 (14) (20–60)	43 (14) (20–90)
90% block T_1/T_0 (s)	52 (31) (20–190)*‡	89 (28) (50–150)	79 (26) (30–160)
Onset time (s)	64 (30) (30–190)*‡	99 (31) (60–180)	106 (38) (40–210)

received randomly, in a double-blind fashion, rocuronium 0.6 mg kg^{-1} ($2\times ED_{95}$), rocuronium 0.9 mg kg^{-1} ($3\times ED_{95}$) or succinylcholine 1 mg kg^{-1}, injected over 15 s into a fast-flowing intravenous infusion of Ringer's solution. No further dose of neuromuscular blocking drug was given.

The times from the end of injection of the neuromuscular blocking drug to the first twitch depression, to 90% block and to the maximum twitch depression (lag time, 90% depression T_1/T_0 and onset time, respectively) and the maximum block were measured. The clinical duration of neuromuscular block at the adductor pollicis muscle was measured using the AMG; after reaching the initial maximum block, train-of-four stimulation was started at the right adductor pollicis muscle every 15 s; times for the first twitch response (T_1/T_0) to return to 25, 75 and 90% and for the TOF to reach 0.7 were measured.

The results are expressed as mean (SD) and range. The physical characteristics of the three groups were compared using analysis of variance (ANOVA) and corrected according to the number of comparisons (Bonferroni), $P<0.05$ was regarded as significant. The pharmacodynamic variables were compared within the groups between the different monitoring sites using the paired-sample t-test, and analysis of variance (ANOVA) was used between groups, corrected for the number of comparisons (Bonferroni); $P<0.05$ was regarded as significant.

The correlation between lag time, 90% block, onset time and maximum effect at the two muscle sites within groups was analysed using Pearson's test; $P<0.05$ was regarded as significant.

Results

Patient characteristics are shown in Table 1. Mean age of the patients was 52 yr (range 20–81), and 65% were female. All patient data in the three groups were comparable and did not show any significant difference. In all patients, determination of supramaximal stimulation at all three monitoring sites was successful and the laryngeal electrode was still attached to the tracheal tube at the time of extubation.

No side-effects due to transcutaneous stimulation of the recurrent laryngeal nerve with a mean current of 40 mA (range 25–55 mA), such as cardiac arrhythmias and skin irritation, were noted. Postoperative laryngoscopic examination did not show any alteration or damage (e.g. haematoma or granuloma) to the vocal cords due to stimulation or placement of the laryngeal electrode.

The mean amplitude of the EMG response to placement of the laryngeal electrode at the adductor laryngeal muscles was 0.9 (0.5) mV (0.4–2 mV) after supramaximal stimulation. Comparison of the onset of neuromuscular blockade at the two monitoring sites showed that, for both drugs, the lag time, 90% block and onset time were significantly shorter at the larynx than at the adductor pollicis, with no significant differences between EMG and AMG measurements ($P<0.01$, Table 2); the mean maximum effect reached at

Table 3 Clinical duration of neuromuscular block at the adductor pollicis muscle for succinylcholine 1 mg kg^{-1}, rocuronium 0.6 mg kg^{-1} and rocuronium 0.9 mg kg^{-1} in 90 patients Mean (SD), *P<0.01, succinylcholine *vs* both doses of rocuronium; †P<0.01, rocuronium 0.6 mg kg^{-1} *vs* rocuronium 0.9 mg kg^{-1}

	Succinylcholine1 mg kg^{-1}	**Rocuronium 0.6 mg kg^{-1}**	**Rocuronium 0.9 mg kg^{-1}**
T$_1$/T$_0$ 25 (min)	7 (2) (4–9)*	35 (12) (17–60)†	53 (22) (11–99)
T$_1$/T$_0$ 75 (min)	8 (2) (5–11)*	38 (7) (24–58)†	66 (25) (32–129)
T$_1$/T$_0$ 90 (min)	9 (3) (5–22)*	45 (20) (21–90)†	74 (29) (36–151)
TOF=0.7 (min)	8 (6) (5–30)*	54 (18) (27–95)†	77 (21) (43–130)

the three sites in the three groups was >93% and did not differ statistically between groups.

The comparison of the pharmacodynamic data for rocuronium compared with succinylcholine showed that the lag times for succinylcholine 1 mg kg^{-1} were not significantly different from those for rocuronium 0.6 and 0.9 mg kg^{-1} at the larynx or for the three drugs at the adductor pollicis muscle, nor was there a significant difference between the rocuronium groups at the two monitoring sites (Table 2).

At the adductor pollicis muscle, 90% block and the onset time were significantly shorter in the succinylcholine group (P<0.01) than in both rocuronium groups (Table 2). The 90% block and onset time of succinylcholine at the larynx were significantly shorter than for both doses of rocuronium, and the times for rocuronium 0.6 mg kg^{-1} were significantly longer than for rocuronium 0.9 mg kg^{-1} (Table 2). There was no correlation of the lag time, 90% block or onset time in the three groups between the larynx and the adductor pollicis muscle.

The clinical duration using AMG at the adductor pollicis muscle is shown in Table 3; the clinical duration was shortest for succinylcholine, followed by rocuronium 0.6 and 0.9 mg kg^{-1}.

Discussion

We have shown that, at the larynx and adductor pollicis muscle, succinylcholine 1 mg kg^{-1} has shorter onset times and a narrower range of effect than both doses of rocuronium, even 0.9 mg kg^{-1}; lag and onset times were shorter at the larynx than at the adductor pollicis muscle. The clinical duration of neuromuscular block, as measured at the adductor pollicis muscle using AMG, was much shorter for succinylcholine, as would be expected.

Evoked electromyographic responses monitored using a disposable surface electrode attached to a tracheal tube were used to measure the onset of block at the larynx. The technique proved reliable in 90 patients and was easy to use without any major technical problems. It was connected to a standard EMG-monitoring device (Multiliner®); recording was performed using modified nerve conduction software, providing not only information about the amplitude of the compound action potential but also about the latency and duration of the signal. It could be recorded in all patients. Since patients were undergoing thyroid surgery, only the onset of neuromuscular block could be measured in this way; monitoring of the duration of the neuromuscular block at the larynx would have meant delaying the start of surgery for almost 1 h in the rocuronium 0.9 mg kg^{-1} group and was therefore omitted. We did, however, monitor nerve integrity in all patients, because the surface laryngeal electrode was used to monitor and identify the recurrent laryngeal nerve intraoperatively. In all patients, a compound action potential could still be traced and recorded after a mean of 2.5 h of surgery. We showed in another study[8] that the surface laryngeal electrode was able to deliver reliable evoked EMG signals for up to 6 h.

All patients were routinely checked 3 days after operation by an otolaryngologist who was not aware of the study, or by the use of the surface electrode, for any lesion or damage to the vocal cords or impairment of vocal cord function; none was found. Transcutaneous stimulation of the laryngeal recurrent nerve was possible in all patients in the same manner as that demonstrated by Donati and colleagues[9] to produce contraction of the adductor laryngeal muscles. No harm from the stimulation, such as burns, skin irritation and cardiac arrhythmia, was noted. The comparison of the two drugs was undertaken for several reasons: rocuronium 0.6 mg kg^{-1} is widely used for intubation in our clinical setting, and provides a peak effect sufficient to ensure good intubation conditions with a reasonable onset time, and rocuronium 0.9 mg kg^{-1} is used in clinical practice to produce onset times equivalent to those given by succinylcholine 1 mg kg^{-1}.

Meistelman and colleagues[10] investigated the onset and duration for rocuronium 0.5 mg kg^{-1} in 14 patients. They found an onset time of 1.4 (0.1) min at the vocal cords with only 77 (5)% maximum blockade; recovery time to 90% T$_1$/T$_0$ was 22±3 min using a cuff pressure method in which the pressure change in the cuff of a tracheal tube placed between the vocal cords was evaluated.

Wright and colleagues[11] used the same method and compared succinylcholine 1 mg kg^{-1} with rocuronium at, among other doses, 0.8 mg kg^{-1}; succinylcholine had a much faster laryngeal onset than rocuronium (34 (12) *vs* 96 (45) s) and a much narrower range of effect (18–58 *vs* 44–183 s), with peak effects similar to those found in the present study.

In a recent study, D'Honneur and colleagues[12] used a specially designed tracheal tube to measure onset and clinical duration for succinylcholine 1 mg kg^{-1} and rocuronium 0.6 mg kg^{-1} at the larynx. There was a much faster onset and shorter duration for succinylcholine than for rocuronium, onset time being 58 (10) s (45–75) *vs* 124 (39) s (70–175) and recovery to 90% T_1/T_0 8.3 (3.2) min (5.7–14.5) *vs* 34.9 (7.6) min (26.3–46.2). This is in concordance with our findings.

Whether a neuromuscular blocking drug can be used to replace succinylcholine for RSI is also related to its clinical duration. It is questionable whether it is important that complete relaxation of the larynx occurs after 47 s, as with succinylcholine 1 mg kg^{-1}, or after 64 s, as with rocuronium 0.9 mg kg^{-1}. However, the return of neuromuscular transmission at the larynx to control levels after 5–10 min or 30–45 min might define whether a patient survives the 'can't intubate–can't ventilate' situation. Another important difference in the onset time of rocuronium in comparison with succinylcholine is the larger interindividual variability. Reliable and sufficient relaxation after a given onset time is more predictable with succinylcholine.

Because of its much longer duration of action and greater interindividual variability, we would not recommend rocuronium 0.9 mg kg^{-1} as a substitute for succinylcholine 1 mg kg^{-1} for RSI, unless there are contraindications to the use of succinylcholine.

References

1 Durant NN, Katz RL. Suxamethonium. *Br J Anaesth* 1982; **54**: 195–208

2 Sparr HJ, Luger TJ, Heidegger T, Putensen-Himmer G. Comparison of intubating conditions after rocuronium and suxamethonium following 'rapid-sequence induction' with thiopentone in elective cases. *Acta Anaesthesiol Scand* 1996; **40**: 425–30

3 Magorian T, Flannery KB, Miller RD. Comparison of rocuronium, succinylcholine, and vecuronium for rapid sequence induction of anesthesia in adult patients [see comments]. *Anesthesiology* 1993; **79**: 913–18

4 Davis WE, Rea JL, Templer J. Recurrent laryngeal nerve localization using a microlaryngeal electrode. *Otolaryngol Head Neck Surg* 1979; **87**: 330–3

5 Maloney RW, Murcek BW, Steehler KW, Sibly D, Maloney RE. A new method for intraoperative recurrent laryngeal nerve monitoring. *Ear Nose Throat J* 1994; **73**: 30–3

6 Khan A, Pearlman, RC, Bianchi DA, Hauck KW. Experience with two types of electromyography monitoring electrodes during thyroid surgery. *Am J Otolaryngol* 1997; **18**: 99–102

7 Srinivasan V, Premachandra DJ. Use of a disposable electrode for recurrent laryngeal nerve monitoring. *J Laryngol Otol* 1998; **112**. 561–4

8 Hemmerling TM, Schurr C, Dern S, Schmidt J, Braun GG, Klein P. IRM-Intraoperatives Recurrensmonitoring als Routinemassnahme in der Schilddrüsenchirurgie. *Der Chirurg* 2000; **71** 545–50

9 Donati F, Plaud B, Meistelman C. A method to measure elicited contraction of laryngeal adductor muscles during anesthesia. *Anesthesiology* 1991; **74**: 827–32

10 Meistelman C, Plaud B, Donati F. Rocuronium (ORG 9426) neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis in humans. *Can J Anaesth* 1992, **39**. 665–9

11 Wright PM, Caldwell JE, Miller RD. Onset and duration of rocuronium and succinylcholine at the adductor pollicis and laryngeal adductor muscles in anesthetized humans. *Anesthesiology* 1994; **81**: 1110–15

12 D'Honneur G, Kirov K, Slavov V, Duvaldestin P. Effects of an intubating dose of succinylcholine and rocuronium on the larynx and diaphragm. *Anesthesiology* 1999, **90**: 951–5

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Cricoid pressure applied after placement of laryngeal mask impedes subsequent fibreoptic tracheal intubation through mask†

T. Asai*, K. Murao and K. Shingu

Department of Anaesthesiology, Kansai Medical University, 10–15 Fumizono-cho, Moriguchi City, Osaka 570-8507, Japan

**Corresponding author*

We studied 70 patients to see if cricoid pressure applied after insertion of the laryngeal mask altered the success rate of tracheal intubation through the mask. After induction of anaesthesia and neuromuscular blockade, patients were randomly allocated to have either cricoid pressure (Group C) or sham pressure (Group S). The view of the glottis through the laryngeal mask was assessed before and after the test pressure, and tracheal intubation through the mask was attempted using a fibreoptic bronchoscope. The test pressure did not alter the view of the glottis in any patient in group S, whereas it narrowed the glottic aperture in 16 out of 35 patients in group C. The fibrescope was inserted into the trachea in all patients in group S and in 25 patients in group C. The success rate of tracheal intubation in group S (31 patients) was significantly higher than in group C (21 patients, $P \ll 0.001$; 95% CI for difference: 9–48%). The time for insertion of the fibrescope in group S (median (95% CI): 12 (11–12) s) was significantly faster than in group C (16 (14–17) s, $P \ll 0.001$; 95% CI for difference: 3–6 s), and the time for tracheal intubation in group S (16 (15–18) s) was significantly faster than in group C (22 (19–24) s, $P<0.0005$; 95% CI for difference: 3–7 s). Cricoid pressure after insertion of the laryngeal mask makes tracheal intubation through the mask significantly more difficult.

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The laryngeal mask$^+$ has a potential role in patients with difficult airways.[1 2] Cricoid pressure is necessary if such a patient is at an increased risk of pulmonary aspiration, as the laryngeal mask cannot reliably prevent gastric insufflation, regurgitation or pulmonary aspiration.[3–5] However, cricoid pressure, when it is applied before insertion, impedes the correct positioning of the laryngeal mask[6–8] and may prevent adequate ventilation.[6 7 9] It has been suggested that cricoid pressure should be released temporarily during insertion of the laryngeal mask and, once the mask has been inserted, cricoid pressure should be reapplied.[7 9]

Cricoid pressure applied after insertion of the laryngeal mask effectively prevents regurgitation[10] and gastric insufflation.[5] The patient is woken up or the trachea intubated through the laryngeal mask, because it is difficult to maintain sufficient force of cricoid pressure for a prolonged period of time,[11] and because ventilation via the laryngeal mask may be insufficient because of the presence of cricoid pressure.[5] Although one of the authors claimed[12] that cricoid pressure applied after insertion of the laryngeal mask did not usually hamper tracheal intubation through the mask, there has been no formal study to confirm this. We studied if this claim was supported.

Patients and methods

We studied 70 patients (ASA physical status class I or II, aged 18–80 yr) undergoing elective surgery, in whom tracheal intubation was indicated. Patients with any pathology of the neck, upper respiratory or upper alimentary tracts, or at risk of pulmonary aspiration of gastric contents were excluded. Patients with Mallampati class 3[13] or 4[14] were also excluded. The institutional research ethics committee approved the study and written informed consent was obtained from all patients.

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In the operating theatre, an electrocardiograph, a pulse oximeter and an arterial pressure cuff were attached. A firm pad (7 cm in height) was placed under the patient's occiput, but not under the neck. After pre-oxygenation, anaesthesia was induced with intravenous thiopental or propofol, and neuromuscular block was produced with vecuronium. Neuromuscular block was monitored with a peripheral nerve stimulator. Anaesthesia was maintained with sevoflurane in oxygen during the study period.

A laryngeal mask was inserted using the method described in the manufacturer's instruction manual.[15] The size 4 was used in all patients for the following reasons. First, several studies[16–19] have shown that size selection based on sex (size 5 in males and size 4 in females) is more appropriate than the weight-based selection described in the instruction manual.[15] Second, the size 4, rather than size 5, was used in males, as the internal diameter of the size 5 is larger than that of size 4,[15] and this difference might alter the success rate of passage of a 6.0-mm-ID tracheal tube through the laryngeal mask into the trachea. The cuff of the mask was inflated with 25 ml of air. This volume was selected because it was the approximate mean minimum volume of air which just prevented gas leak around the mask,[16] and because further inflation of the cuff by the maximum volume (30 ml) provides less effective sealing.[17]

Adequacy of ventilation was assessed by manual ventilation. Ventilation was judged as adequate when chest inflation suggested a satisfactory compliance. If it was not possible to ventilate the lungs adequately, one more attempt at placement of the laryngeal mask was allowed. If unsuccessful, the patient was excluded from the study. After successful insertion, a bite-block (a wad of gauze) was inserted, and both the laryngeal mask and the bite-block were fixed to the patient's face with tape.

A 6.0-mm reinforced tracheal tube (Mallinckrodt, Athlone, Ireland) was inserted into the laryngeal mask, and a fibreoptic bronchoscope (Olympus, outer diameter: 3.5 mm) was passed through them. The view of the larynx was assessed by looking through the bronchoscope with its tip positioned at the level of the grille of the mask. The patient was included if only the glottis or the glottis and tip of the epiglottis were seen; the patient was excluded if the epiglottis was pressed downward or if the glottis was not seen.

Patients were randomly allocated to one of two groups by block randomization (in blocks of 10). In one group (Group C), cricoid pressure was applied by an assistant, whereas in the other group (Group S), the assistant placed fingers on the cricoid cartilage, but applied no pressure (sham pressure). In both groups, the assistant placed a free hand under the patient's neck (i.e. bimanual cricoid pressure). When applying the test pressure, no efforts were made to extend the patient's head on the neck. The assistant who applied cricoid pressure had been trained to generate ~30 N by practising on a weighing scale,[20] and the scale was used before each case to standardize the pressure as much as possible. The investigator who attempted to intubate through the laryngeal mask was blind as to whether or not cricoid pressure was being applied, by covering the patient's neck and the assistant's hands with a drape. The change in the patency of the glottis was assessed after application of the test pressure (1 = no or mild change; 2 = the anterior part of the glottis was narrowed; 3 = the entire part of the glottis was narrowed; 4 = glottis not seen).

The fibreoptic bronchoscope was then inserted into the trachea and the tracheal tube was passed over the fibrescope into the trachea. If it was difficult to insert the tracheal tube into the trachea, rotation of the tube (clockwise, possibly followed by anticlockwise rotation) and alteration of the position of the patient's head and neck were allowed. Only one attempt with the maximum duration of 120 s was allowed for tracheal intubation.

Statistics

Fisher's exact test was used to compare the success rate of tracheal intubation between groups. A value of $P<0.05$ was considered significant. The 95% confidence intervals (CI) for difference in the success rate of tracheal intubation between groups were also calculated.

Time for insertion of the fibrescope into the trachea and time for tracheal intubation over the fibrescope were measured in patients in whom tracheal insertion of the fibrescope or tracheal intubation succeeded. The normal plots (plots of normal scores) and Shapiro–Francia W′ test (which analyses if the data are normally distributed)[21] showed that the time for insertion of the fibrescope or tracheal intubation was generally not normally distributed. The Mann–Whitney *U*-test was therefore used to compare the time for insertion of the fibrescope and time for tracheal intubation between groups. The 95% CI for each time and CI for time difference between groups were also calculated.

In our previous studies, when cricoid pressure was applied, the success rate of tracheal intubation through the laryngeal mask was 90–95%.[6 22] Our hypothesis was that cricoid pressure applied after insertion of the mask would not alter the success rate of tracheal intubation through the mask, with a difference in the success rate of up to 20%. Sixty to seventy patients would be required to assess this hypothesis, with a power of 90% and a one-sided 95% confidence interval, using an equivalence test.[23]

Results

In 72 of the patients recruited, adequate ventilation through the laryngeal mask was obtained at the first attempt; however, in two patients the epiglottis was pressed downward by the mask and these patients were excluded from the study. The remaining 70 patients were studied. The height, weight, sex ratio and age of patients were similar in the two groups (Table 1).

Table 1 Patients' characteristics (mean (SD); age (range)) and the proportion of the view of the larynx through the laryngeal mask before application of the test pressure A = the glottis, but not the tip of the epiglottis, seen; Ba = the glottis and tip of the epiglottis seen[7]

	Sham pressure	Cricoid pressure
n	35	35
Age (yr)	50 (20–76)	54 (23–80)
Sex (M:F)	21:14	23.12
Weight (kg)	61 (11)	61 (11)
Height (cm)	162 (7)	162 (9)
View of the glottis (A Ba)	33:2	32:3

After application of the test pressure, the view of the glottis was not altered in any patient in group S, whereas it deteriorated in 16 out of 35 patients (46%) in group C (score 2: five patients; score 3: three patients; and score 4: eight patients). The fibrescope was inserted into the trachea in all patients in group S, whereas it succeeded in 25 patients in group C (Fig. 1). Tracheal intubation succeeded in 31 patients (89%) in group S and in 21 patients (60%) in group C; there was a significant difference in its success rate between groups ($P \ll 0.001$; 95% CI for difference: 9–48%, Fig. 1).

In patients in whom insertion of the fibrescope into the trachea succeeded, the time for insertion of the fibrescope in group S (median (95% CI): 12 (11–12) s) was significantly faster than in group C (16 (14–17) s, $P \ll 0.001$; 95% CI for difference: 3–6 s). Similarly, in patients in whom tracheal intubation succeeded, the time for tracheal intubation in group S (16 (15–18) s) was significantly faster than in group C (22 (19–24) s, $P<0.0005$; 95% CI for difference: 3–7 s).

Discussion

Contrary to our hypothesis, cricoid pressure applied after insertion of the laryngeal mask significantly decreased the success rate and the ease of tracheal intubation through the laryngeal mask.

When cricoid pressure is applied without an undue force (~30 N) in the absence of the laryngeal mask, the pressure usually does not worsen and may improve the view of the glottis at laryngoscopy.[20] In contrast, in our study in the presence of the laryngeal mask, cricoid pressure applied at 30 N frequently narrowed the glottis and made tracheal intubation through the mask more difficult (Fig. 2). This difference is likely to be produced by the laryngeal mask.

The distal part of the laryngeal mask occupies the hypopharynx (laryngeal part of the pharynx) and the tip of the mask reaches the caudal border of the cricoid cartilage. Inflation of the cuff shifts the larynx anteriorly.[2] When cricoid pressure is applied in the presence of the laryngeal mask, the caudal part of the larynx (or the cricoid cartilage) is shifted back against the posterior pharyngeal wall while theoretically the cranial part of the larynx (or more specifically, the arytenoid cartilage) is being shifted anteriorly by the mask, tilting the larynx anteriorly and closing the glottis (Fig. 2). In contrast, when the laryngeal mask is not inserted, because there is little space between the larynx and pharyngeal wall, there would only be a slight displacement of the larynx with cricoid pressure (Fig. 3).

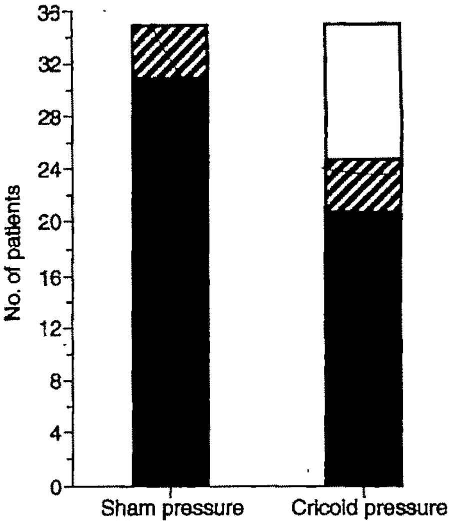

Fig 1 Success rate of insertion of tracheal intubation through the laryngeal mask using a fibre optic bronchoscope with and without cricoid pressure applied after insertion of the mask. Tracheal intubation through the laryngeal mask succeeded (filled box), tracheal insertion of a fibrescope succeeded, but tracheal intubation failed (hatched box) and tracheal insertion of a fibrescope failed (clear box).

In one report, a tilted larynx with a closed glottis was observed in one out of 85 patients in whom cricoid pressure was applied before insertion of the laryngeal mask.[24] It seems likely that the mask wedged behind the cricoid cartilage despite application of cricoid pressure and the mask caused the obstruction. In our study, where cricoid pressure was applied after insertion of the laryngeal mask, the glottis was narrowed more frequently, supporting this theory. This narrowing of the glottis is also consistent with a previous report that cricoid pressure applied after insertion of the laryngeal mask inhibited ventilation via the mask.[5]

Fibrescope-aided tracheal intubation through the laryngeal mask is significantly easier and faster than conventional fibreoptic intubation (without the aid of the laryngeal mask). With conventional fibreoptic tracheal intubation, advance of the tracheal tube over the fibrescope into the trachea is difficult in 50–90% of patients even if the patients do not have difficult airways.[22 25 26] In contrast, insertion of the fibrescope through the laryngeal mask into the trachea and advance of the tracheal tube over the fibrescope are usually easy.[6 20] In our current study, the success rate of fibreoptic intubation through the laryngeal mask (without application of cricoid pressure) was 89%, consistent with previous reports (success rates 90 or 95%).[6 22] There have also been case reports of successful and smooth fibreoptic intubation through the laryngeal mask in patients in whom conventional fibreoptic intubation had failed or was extremely

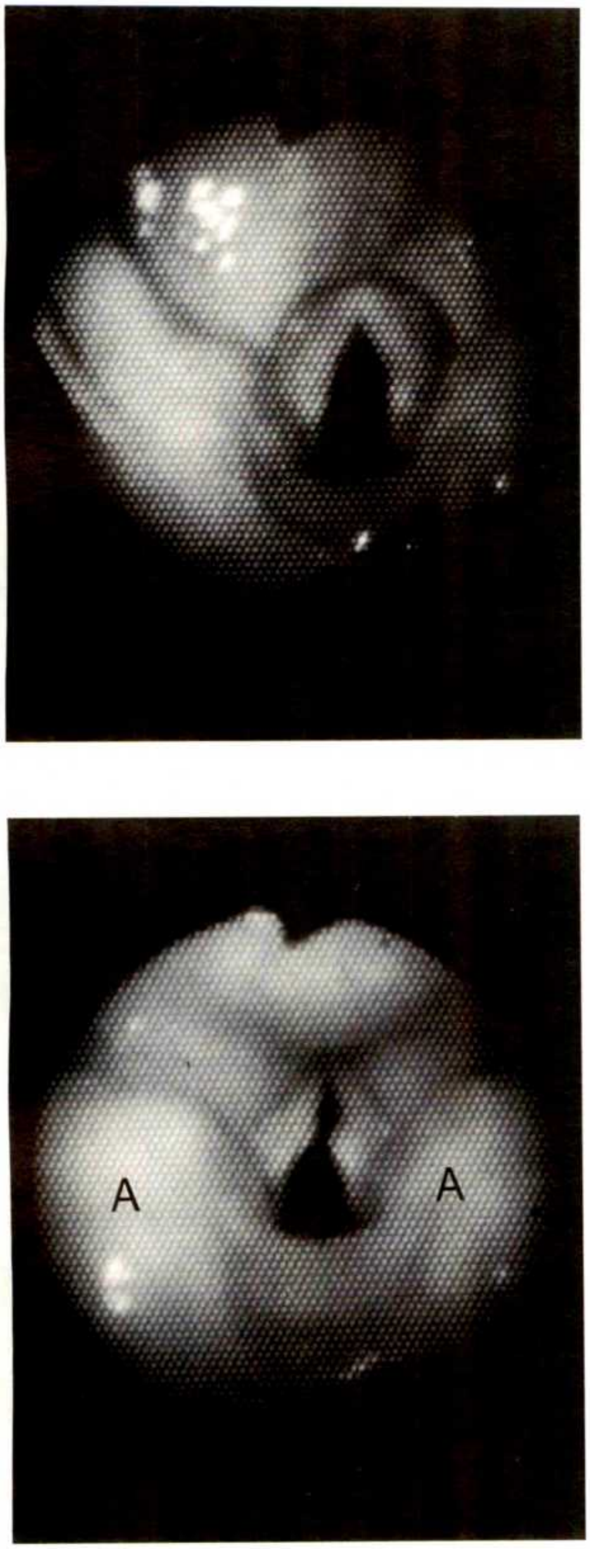

Fig 2 A typical view of the glottis through the laryngeal mask, before (upper figure) and after (lower figure) application of cricoid pressure. The presence of the laryngeal mask shifts the entire part of the larynx anteriorly. Cricoid pressure shifts the lower part of the larynx back towards the posterior pharyngeal wall, while the upper part remained shifted anteriorly, causing the anterior tilting of the larynx. A = tissue covering the arytenoid cartilages.

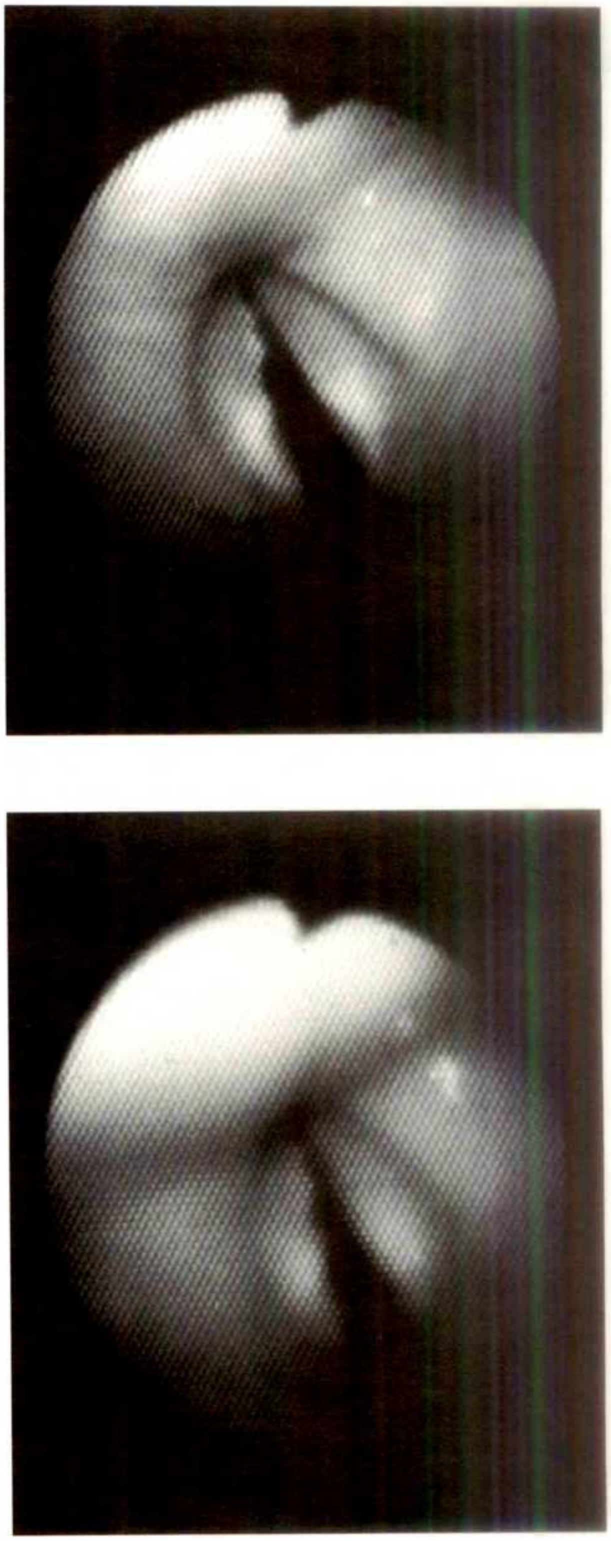

Fig 3 A typical view of the glottis, before (upper figure) and after (lower figure) application of cricoid pressure (without the presence of the laryngeal mask). There is little difference in the patency of the glottis.

difficult.[27 28] Therefore, the laryngeal mask is a useful aid to fibrescope-aided tracheal intubation.

In our previous report in which cricoid pressure was applied before insertion of the laryngeal mask, the success rate of fibreoptic tracheal intubation through the laryngeal mask was 15% (three out of 20 patients) and release of the pressure (after insertion of the mask) only allowed tracheal intubation in another four patients (20%).[6] In our current study, in which cricoid pressure was applied after insertion of the laryngeal mask, the success rate of tracheal intubation was 60% (21 out of 35 patients). Therefore, cricoid pressure, regardless of the timing of application, impedes tracheal intubation through the laryngeal mask, and it can be concluded that the usefulness of the laryngeal mask as the aid to tracheal intubation is markedly reduced in patients at increased risk of pulmonary aspiration.

The role of the laryngeal mask has been established in patients with difficult airways, but there has been uncertainty about its role when patients are also at increased risk of pulmonary aspiration. We propose its use in such patients in the following three situations. The first situation is when tracheal intubation has failed but ventilation via a facemask is possible after induction of anaesthesia. Although there is generally no need to insert the laryngeal mask in this situation, the laryngeal mask might be usefully inserted prior to intubation through it.[1 2] However, in patients at increased risk of pulmonary aspiration, attempt should not be made to insert the laryngeal mask, because cricoid pressure often impedes its correct insertion, and because even if the laryngeal mask has been successfully inserted, cricoid pressure often prevents tracheal intubation through the mask.

The second situation is when tracheal intubation using a laryngoscope has failed and adequate ventilation through a facemask is impossible after induction of anaesthesia. In this situation, insertion of the laryngeal mask may be attempted while equipment for transtracheal ventilation is being prepared. Cricoid pressure should be temporarily loosened during insertion of the laryngeal mask to increase the success rate of insertion, although this temporary release may allow regurgitation and pulmonary aspiration.[6 7 9] Cricoid pressure should be reapplied after insertion of the mask, as it effectively prevents regurgitation of gastric contents.[10] If tracheal intubation is required, it may be attempted through the laryngeal mask while cricoid pressure is kept applied, and if there is difficulty in advancing the tracheal tube over the fibrescope, cricoid pressure might be temporarily loosened and tracheal intubation over the fibrescope reattempted.

The third situation is when a difficult tracheal intubation is predicted. One of the authors reported previously the method of awake insertion of the laryngeal mask, and subsequent tracheal intubation through the mask before or after induction of anaesthesia, in patients with full stomachs.[29] However, we no longer recommend the latter method, as our current study has shown that tracheal intubation through the laryngeal mask becomes more difficult when cricoid pressure is applied. Therefore, it is safer to intubate the trachea before induction of anaesthesia.

References

1 Benumof JL. Laryngeal mask airway and the ASA difficult airway algorithm. *Anesthesiology* 1996; **84**: 686–99

2 Asai T, Morris S. The laryngeal mask airway: its features, effects and role. *Can J Anaesth* 1994; **41**: 930–60

3 Devitt JH, Wenstone R, Noel AG, O'Donnell MP. The laryngeal mask airway and positive-pressure ventilation. *Anesthesiology* 1994; **80**: 550–5

4 Nandi M, Maltby JR. Vomiting and aspiration pneumonitis with the laryngeal mask airway. *Can J Anaesth* 1992; **39**: 69–70

5 Asai T, Barclay K, McBeth C, Vaughan RS. Cricoid pressure applied after placement of the laryngeal mask prevents gastric insufflation but inhibits ventilation. *Br J Anaesth* 1996; **76**: 772–6

6 Asai T, Barclay K, Power I, Vaughan RS. Cricoid pressure impedes placement of the laryngeal mask airway and subsequent tracheal intubation through the mask. *Br J Anaesth* 1994; **72**: 47–51

7 Asai T, Barclay K, Power I, Vaughan RS. Cricoid pressure impedes placement of the laryngeal mask airway. *Br J Anaesth* 1995; **74**: 521–5

8 Aoyama K, Takenaka I, Sata T, Shigematsu A. Cricoid pressure impedes positioning and ventilation through the laryngeal mask airway. *Can J Anaesth* 1996; **43**: 1035–40

9 Ansermino JM, Blogg CE. Cricoid pressure may prevent insertion of the laryngeal mask airway. *Br J Anaesth* 1992; **69**: 465–7

10 Strang TI. Does the laryngeal mask airway compromise cricoid pressure? *Anaesthesia* 1992; **47**: 829–31

11 Meek T, Vincent A, Duggan JE. Cricoid pressure: can protective force be sustained? *Anaesthesia* 1998; **80**: 672–4

12 Asai T. The laryngeal mask airway as an aid to intubate in patients at risk of aspiration? *Anesthesiology* 1993; **78**: 1198

13 Mallampati SR, Gatt SP, Gugino LD, *et al.* A clinical sign to predict difficult tracheal intubation: a prospective study. *Can Anaesth Soc J* 1985; **32**: 429–34

14 Samsoon GLT, Young JRB. Difficult tracheal intubation: a retrospective study. *Anaesthesia* 1987; **42**: 487–90

15 Brimacombe JR, Brain AIJ, Berry AM. *The Laryngeal Mask Airway Instruction Manual.* Berkshire, UK: Intavent Research Limited, 1997

16 Asai T, Howell TK, Koga K, Morris S. Appropriate size and inflation of the laryngeal mask airway. *Br J Anaesth* 1998; **80**: 470–4

17 Brimacombe J, Keller C. Laryngeal mask airway size selection in males and females: ease of insertion, oropharyngeal leak pressure, pharyngeal mucosal pressures and anatomical position. *Br J Anaesth* 1999; **82**: 703–7

18 Berry AM, Brimacombe JR, McManus KF, Goldblatt M. An evaluation of the factors influencing selection of the optimal size of the laryngeal mask airway in normal adults. *Anaesthesia* 1998; **53**: 565–70

19 Voyagis GS, Batzioulis PG, Secha-Doussaitou PN. Selection of the proper size of laryngeal mask airway in adults. *Anesth Analg* 1996; **83**: 663–4

20 Vanner RG, Asai T. Safe use of cricoid pressure. *Anaesthesia* 1999; **54**: 1–3

21 Altman DG. *Practical Statistics for Medical Research.* London: Chapman and Hall, 1991

22 Koga K, Asai T, Latto IP, Vaughan RS. Effect of the size of a tracheal tube and the efficacy of the use of the laryngeal mask for

fibrescope-aided tracheal intubation. *Anaesthesia* 1997; **52**: 131–5

23 Armitage P, Berry G. *Statistical Methods in Medical Research*, 3rd edn. Oxford: Blackwell Scientific, 1994

24 Brimacombe J, Berry A. Mechanical airway obstruction after cricoid pressure with the laryngeal mask airway. *Anesth Analg* 1994; **78**: 604–5

25 Schwartz D, Johnson C, Roberts J. A maneuver to facilitate flexible fiberoptic intubation. *Anesthesiology* 1989; **71**: 470–1

26 Marsh NJ. Easier fiberoptic intubations. *Anesthesiology* 1992; **76**: 860–1

27 Asai T. Fiberoptic tracheal intubation through the laryngeal mask in an awake patient with cervical spine injury. *Anesth Analg* 1993; **77**: 404

28 Asai T. Use of the laryngeal mask for fibrescope-aided tracheal intubation in an awake patient with a deviated larynx. *Acta Anaesthesiol Scand* 1994; **38**: 615–6

29 Asai T. Use of the laryngeal mask for tracheal intubation in patients at increased risk of aspiration of gastric contents. *Anesthesiology* 1991; **77**: 1029–30

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Mucosal pressure and oropharyngeal leak pressure with the ProSeal *versus* laryngeal mask airway in anaesthetized paralysed patients

C. Keller[1] and J. Brimacombe[2]*

[1]*Department of Anaesthesia and Intensive Care Medicine, Leopold-Franzens University, 6020, Innsbruck, Austria.* [2]*University of Queensland, Department of Anaesthesia and Intensive Care, Cairns Base Hospital, Australia*

**Corresponding author*

The ProSeal laryngeal mask airway (PLMA) is a new laryngeal mask device with a larger, wedge-shaped cuff and a drainage tube. We tested the hypothesis that directly measured mucosal pressure and oropharyngeal leak pressure (OLP) are higher for the PLMA compared with the laryngeal mask airway (LMA†). We also assess the mechanism of seal, and the reliability of cuff volume, *in vivo* intracuff pressure and calculated mucosal pressure (*in vivo* minus *in vitro* intracuff pressure) to predict directly measured mucosal pressure. Thirty-two anaesthetized, paralysed adult patients were randomly allocated to receive either a size 4 LMA or PLMA. Microchip sensors were attached at locations corresponding to: (a) base of tongue; (b) distal oropharynx; (c) hypopharynx; (d) lateral pharynx; (e) posterior pharynx; and (f) pyriform fossa. *In vitro* and *in vivo* intracuff pressures, OLP and directly measured mucosal pressure were documented at zero volume and after each 10 ml up to 40 ml. Directly measured mucosal pressure was similar between devices for a given cuff volume, but was lower for the PLMA for a given OLP. Directly measured mucosal pressure was highest in the distal oropharynx for both devices, but rarely (<5%) exceeded 35 cm H_2O. OLP was higher for the PLMA at all cuff volumes. Directly measured mucosal pressure was usually lower than OLP for both devices, and there was a positive correlation between directly measured mucosal pressure and OLP. Cuff volume, *in vivo* intracuff pressure and calculated mucosal pressure were poor to moderate predictors of directly measured mucosal pressure for the LMA and PLMA. We conclude that the PLMA forms a better seal than the LMA without an increase in directly measured mucosal pressure.

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The ProSeal laryngeal mask airway (PLMA) is a new laryngeal mask device with a larger cuff and a drainage tube. The cuff has a flat dorsal component designed to press the ventral elliptical cuff more firmly into the periglottic tissues and a wedge-shaped proximal component designed to plug gaps in the proximal pharynx (Fig. 1). We considered that these structural differences would influence the way the cuff interacted with the pharyngeal tissues. In this study, we test the hypothesis that directly measured mucosal pressure and oropharyngeal leak pressure (OLP) are higher for the PLMA compared with the classic laryngeal mask airway (LMA†) in anaesthetized, paralysed patients. We also assess the mechanism of seal, and the reliability of cuff volume, *in vivo* intracuff pressure and calculated mucosal pressure to predict directly measured mucosal pressure.

Methods

Thirty-two ASA 1–2 adult patients were randomly allocated by opening a sealed envelope to receive either the LMA (eight male; eight female) or PLMA (eight male; eight female) for airway management. Ethical committee approval and informed consent were obtained. Patients were excluded if they were at risk of aspiration. Directly measured mucosal pressure was measured using six 1.2-mm-diameter strain gauge silicone microchip sensors (Codman® MicroSensor™, Johnson and Johnson Medical, Bracknell, UK) attached to the external surface of the

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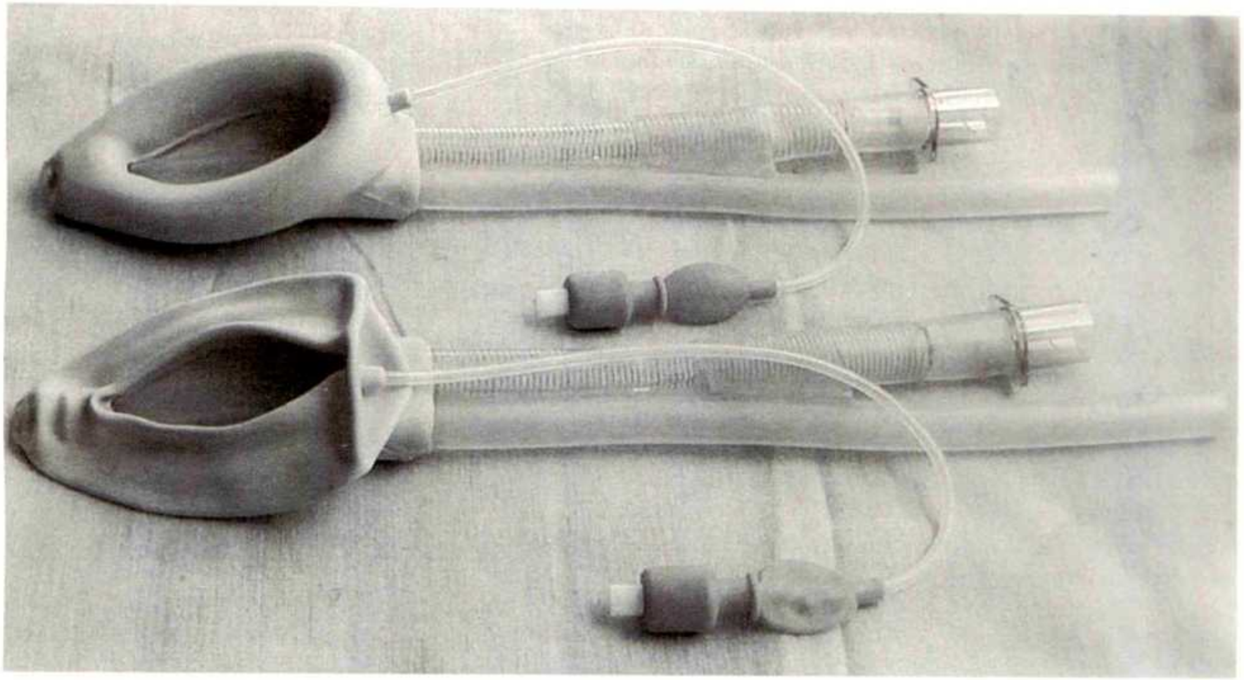

Fig 1 The PMA with the cuff inflated and deflated.

LMA/PLMA with clear adhesive dressing 0.45 mm thick (Tegaderm™, 3M, Ontario, Canada), as previously described.[1 2] The sensors were attached to the following locations (corresponding mucosal areas): (a) anterior base of cuff (base of tongue); (b) posterior tube (distal oropharynx); (c) posterior tip of cuff (hypopharynx); (d) posterior middle part of the cuff side (lateral pharynx); (e) middle of the backplate or dorsal cuff (posterior pharynx); and (f) anterior middle part of the cuff side (pyriform fossa) (Fig. 2A,B). The sensing element of the sensor was orientated towards the mucosal surface and was accurate to ±2%. The position/orientation/accuracy of all the sensors were checked over the entire inflation range *in vitro* before and after use in each patient.[1 2] Four LMAs and four PLMAs were used during the study. All LMA devices had passed the pre-use check tests.[3]

Anaesthesia was induced with propofol 2.5 mg kg^{-1} and maintained with 100% oxygen and 1–2% sevoflurane. Muscle relaxation was achieved with atracurium 0.5 mg kg^{-1}. An experienced LMA user inserted/fixed the LMA/PLMA using the technique recommended for the LMA.[3] Both devices were fixed by taping the tube over the chin. The numbers of attempts taken to place the device were recorded. A failed attempt was defined as removal of the device from the mouth. A size #4 LMA/PLMA was used for all patients. The pilot balloon was attached via a three-way tap to a 10-ml syringe and a calibrated pressure transducer accurate to ±5%. The intracuff pressure was reduced to –40 cm H_2O *in vitro*. *In vitro* and *in vivo* intracuff pressures, OLP and directly measured mucosal pressure were documented at zero volume and after each additional 10 ml up to 40 ml.

When measurements were complete, fibreoptic position was determined at 20 ml cuff volume to provide general information about anatomical position. OLP was measured by closing the expiratory valve of the circle system at a fixed gas flow of 3 litre min^{-1}, and noting the airway pressure at which the dial on the anaeroid manometer reached equilibrium.[4] Fibreoptic position was determined using an established scoring system (4 = only vocal cords visible; 3 = vocal cords plus posterior epiglottis; 2 = vocal cords plus anterior epiglottis; 1 = vocal cords not seen.[5 6] The position of the anterior tip sensor was verified at the end of the procedure by observation of a pressure spike during the application of cricoid pressure. An unblinded observer made measurements with the head–neck in the neutral position with the occiput resting on a firm pillow 7 cm in height.

Calculated mucosal pressure was determined by subtracting the *in vivo* intracuff pressure measurements from the *in vitro* intracuff pressure measurements, as previously described.[7] The mechanism of seal was determined by analysing the relationship between cuff volume, OLP and directly measured mucosal pressure. It was assumed that if OLP was greater than directly measured mucosal pressure, the mechanism of seal was related to the matching shape of the cuff and pharynx; and if there was a positive correlation between OLP and directly measured mucosal pressure, the mechanism of seal was related to the pressure exerted by the cuff against the pharyngeal mucosa.

Statistics

Sample size was selected to detect a projected difference of 25% between the groups with respect to directly measured mucosal pressure for a type I error of 0.05 and a power of 0.9. The power analysis was based on data from a pilot study of 10 patients in which directly measured mucosal pressure was measured with the PLMA and a previous study of directly measured mucosal pressure with the LMA.[1] The distribution of data was determined using Kolmogorov–Smirnov analysis.[8] Statistical analysis was with paired *t*-test (normally distributed data), chi-squared test (non-parametric data), Friedman's two-way analysis of variance (non-normally distributed data) and regression analysis. The relationship between directly measured mucosal pressure and other variables was determined using Pearson product-moment correlation coefficient. The reliability of *in vivo* intracuff and calculated mucosal pressure to predict directly measured mucosal pressure was analysed using the intraclass correlation coefficient (ICC).[9 10] Significance was taken as $P<0.05$. Statistical analysis was performed on an IBM computer using SYSTAT version 7.0.

Results

The mean (range) for age, height and weight was 35 (19–65) yr, 169 (150–192) cm and 67 (40–95) kg, respectively. The physical characteristics of the patients in the two groups were similar. The first time success rate for the LMA and PLMA was 16/16 and 14/16. One patient with the PLMA required two attempts due to malposition (tip in the glottic inlet), and one patient required two attempts due to resistance when manoeuvring the cuff from the mouth to the pharynx. The pressure from the anterior tip probe increased to >100 cm H_2O when cricoid pressure was applied in all patients. The position/orientation/accuracy of the sensors were identical before and after usage. Directly measured mucosal pressure at specific locations was generally similar for the LMA and PLMA (Table 1). The lowest directly measured mucosal pressure for both devices was in the lateral pharynx, and the highest in the posterior pharynx and distal oropharynx. OLP was higher for the PLMA compared with the LMA at all cuff volumes (Table 1). OLP for both devices increased with increasing intracuff volume from 0 to 10 ml, but did not change from 10 to 20 ml, 20 to 30 ml or 30 to 40 ml. When comparing directly measured mucosal pressure with OLP at all cuff volumes and locations, directly measured mucosal pressure was significantly lower than OLP on 19/30 occasions for the LMA and 25/30 occasions for the PLMA, and directly measured mucosal pressure was never significantly higher than OLP for either device. There was a positive correlation between directly measured mucosal pressure and OLP at 3/6 locations with the LMA, at 4/6 locations with the PLMA, and a negative correlation at 1/6 locations with the PLMA (Table 2). There was a positive correlation between directly measured mucosal pressure and OLP at all cuff volumes for both the LMA and PLMA (all $P<0.001$, Table 2). Fibreoptic position (*n*: 4/3/2/1) for the LMA was 11/2/2/1 and for the PLMA was 5/7/3/2. There was a significant increase in directly measured mucosal pressure with increasing cuff volume, *in vivo* intracuff pressure and calculated mucosal pressure at all locations for both devices; apart from the PLMA in the distal oropharynx which had a significant decrease (Table 3).

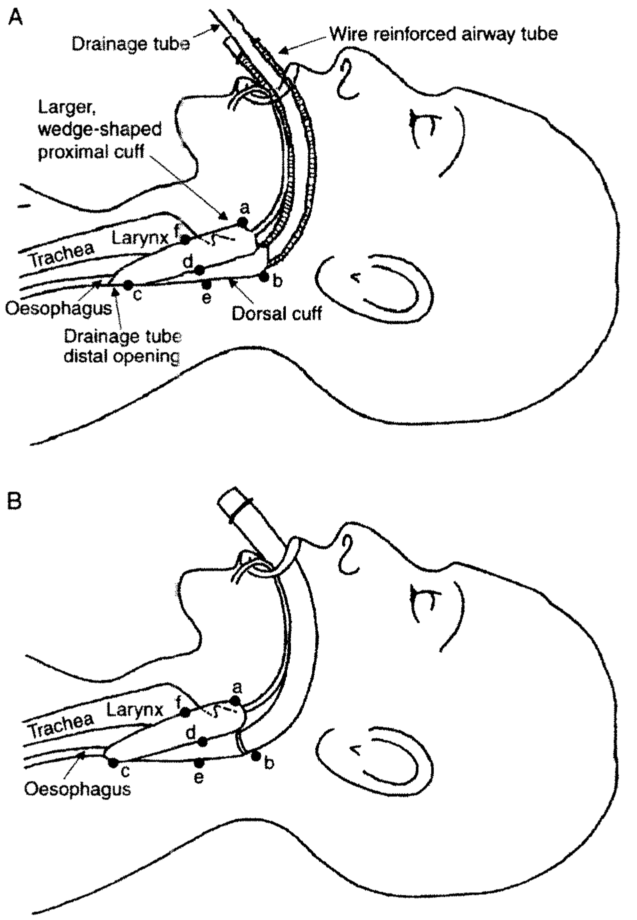
A
Drainage tube
Wire reinforced airway tube
Larger, wedge-shaped proximal cuff
a
Larynx
f
Trachea
d
b
c
e
Oesophagus
Dorsal cuff
Drainage tube distal opening
B
a
Larynx
f
Trachea
d
b
c
e
Oesophagus

Fig 2 Schematic diagram showing the location of sensors (corresponding mucosal area) on the PMA (A) and Classic (B) LMA. (a) Anterior base of cuff (base of tongue); (b) posterior tube (distal oropharynx); (c) the posterior tip of cuff (hypopharynx); (d) posterior middle part of the cuff side (lateral pharynx); (e) the middle of the backplate or dorsal cuff (posterior pharynx); and (f) anterior middle part of the cuff side (pyriform fossa).

Discussion

Directly measured mucosal pressure was similar for both devices (Table 1) and lower than the upper limit considered safe for the tracheal mucosa during prolonged intubation (41 cm H_2O).[11] We recently showed that pharyngeal mucosal perfusion is progressively reduced when directly measured mucosal pressure is increased from 34 to 80 cm H_2O.[12] Directly measured mucosal pressure in the current study rarely exceeded 34 cm H_2O, suggesting that mucosal ischaemic injury will be uncommon with either device. However, the manufacturer recommends that LMA cuff volume is reduced to the minimal required to form an

Table 1 OLP, *in vivo*, *in vitro* and calculated intracuff pressure and directly measured pharyngeal mucosal pressures with increasing cuff volume for the standard LMA and PLMA. Data are mean (95% CI). Pressures are in cm H_2O. Interdevice statistics LMA *versus* PLMA. Location B $^{a}P=0.02$; $^{b}P=0.04$. Location C $^{c}P=0.04$. Location F. $^{d}P=0.04$, $^{e}P=0.04$

	Vol. (ml)	OLP	Intracuff pressures		Mucosal pressures						
			In vitro (*n* = 40)	*In vivo*	Calculated	Directly measured					
						A (base of tongue)	B (distal oropharynx)	C (hypopharynx)	D (lateral pharynx)	E (posterior pharynx)	F (pyriform fossa)
LMA	0	6 (4–9)	–40	–30 (–33–27)	10 (8–12)	4 (1–7)	2 (1–4)^{a}	1 (0–3)	1 (0–2)	2 (1–3)	6 (4–8)^{d}
	10	15 (11–19)	–8 (–9–7)	20 (16–23)	25 (21–29)	5 (1–10)	8 (4–13)	5 (2–8)	1 (1–2)	3 (2–5)	7 (5–9)^{e}
	20	17 (13–20)	–3 (–4–2)	87 (75–99)	77 (64–90)	11 (6–16)	15 (6–24)	9 (5–13)	2 (1–4)	4 (2–5)	7 (5–9)
	30	17 (13–20)	126 (124–128)	223 (211–236)	87 (72–101)	14 (9–19)	14 (7–20)	12 (6–17)	2 (1–4)	7 (3–12)	10 (5–9)
	40	16 (12–19)	243 (240–246)	320 (308–333)	71 (55–87)	15 (10–21)	17 (9–26)^{b}	15 (10–21)^{c}	4 (2–6)	12 (6–17)	11 (7–16)
PLMA	0	18 (14–22)	–40	–34 (–37–31)	6 (4–8)	5 (–3–13)	22 (6–35)^{a}	2 (0–5)	4 (0–7)	2 (0–4)	1 (0–3)^{d}
	10	24 (20–28)	–12 (–11–3)	22 (19–26)	30 (26–35)	5 (–2–12)	20 (6–35)	6 (2–10)	5 (1–10)	8 (-2–19)	2 (0–4)^{e}
	20	25 (21–29)	–7 (–7–6)	49 (42–56)	46 (38–53)	9 (2–16)	16 (5–26)	8 (4–12)	6 (2–10)	16 (–2–35)	5 (1–9)
	30	26 (21–31)	5 (4–5)	93 (83–102)	79 (66–92)	11 (4–19)	11 (–3–18)	7 (4–11)	6 (2–11)	18 (3–32)	7 (–1–15)
	40	27 (21–32)	40 (39–41)	139 (128–151)	93 (76–110)	16 (8–25)	6 (1–12)^{b}	7 (3–11)^{c}	6 (2–11)	20 (3–38)	8 (–1–17)

Table 2 PPCC and ICC for directly measured mucosal pressures with oropharyngeal leak pressure for the LMA and PLMA by location and volume. PPCC. +1 = perfect positive correlation; 0 = no correlation, –1 = perfect negative correlation ICC ≥0.75 = excellent reliability; 0.41–0.74 = moderate reliability; <0.40 = poor.[10] NS, not significant

	LMA			PLMA		
	PPCC	*P*	ICC	PPCC	*P*	ICC
(a) Base of tongue	0.210	NS	0.33	0.415	0.01	0.38
(b) Distal oropharynx	0.302	NS	0.39	–0.519	0.001	0.54
(c) Hypopharynx	0.450	0.01	0.46	0.221	NS	0.33
(d) Lateral pharynx	0.301	NS	0.40	0.290	NS	0.35
(e) Posterior pharynx	0.402	0.01	0.44	0.410	0.01	0.49
(f) Pyriform fossa	0.402	0.01	0.45	0.383	0.04	0.45
Cuff volume						
0 ml	0.586	0.001	0.52	0.410	0.001	0.49
10 ml	0.600	0.001	0.54	0.421	0.001	0.48
20 ml	0.602	0.001	0.55	0.424	0.001	0.47
30 ml	0.599	0.001	0.52	0.410	0.001	0.47
40 ml	0.596	0.001	0.51	0.402	0.001	0.45

effective seal.[3] Because the PLMA forms a more effective seal than the LMA at all cuff volumes, directly measured mucosal pressure would be lower for the PLMA if this recommendation was applied. This may have implications for the incidence of pharynolaryngeal morbidity between devices.

The PLMA forms a more effective seal with the upper airway than the LMA. The PLMA was designed so that the larger, wedge-shaped cuff would plug gaps in the proximal pharynx and the flat dorsal cuff would push the ventral cuff more firmly into the periglottic tissues. We found no evidence (in terms of directly measured mucosal pressure change) that the ventral cuff was being pushed more firmly into the periglottic tissues, and we consider that the wedge-shaped proximal cuff is the more important new design feature with respect to improved seal. This latter concept is supported by the fact that OLP was higher at zero cuff volume when the dorsal cuff is deflated. Directly measured mucosal pressure increased with cuff volume at all locations except in the distal oropharynx with the PLMA where it decreased (Table 1). A possible explanation is that the distal posterior tube of the PLMA moves proximally during cuff inflation from the relatively narrow proximal laryngopharynx to the broader oropharynx.

The pattern of change of OLP with increasing cuff volume was similar for both devices suggesting that the mechanism of seal is similar. Directly measured mucosal pressure was generally lower than OLP, and there was a positive correlation between directly measured mucosal pressure and OLP. This suggests that the mechanism of seal is not only related to the matching shape of the cuff and pharynx, but also to the pressure exerted by the cuff against the mucosa. In a previous study,[13] we suggested that the mechanism of seal was related to the matching shape of the

Table 3 PPCC and ICC for directly measured mucosal pressures with cuff volume, *in vivo* intracuff pressure and calculated mucosal pressure for the LMA and PLMA PPCC: +1 = perfect positive correlation, 0 = no correlation; −1 = perfect negative correlation ICC ≥0.75 = excellent reliability, 0.41–0.74 moderate reliability; <0.40 = poor[10] NS, not significant

		Cuff volume			***In vivo* intracuff pressure**		**Calculated mucosal pressure**			
Device	**Location**	**PPCC**	***P*-value**	**ICC**	**PPCC**	***P*-value**	**ICC**	**PPCC**	***P*-value**	**ICC**
LMA	(a) Base of tongue	0.627	<0.001	0.49	0.650	<0.001	0.48	0.609	<0.001	0.45
	(b) Distal oropharynx	0.539	<0.001	0.48	0.573	<0.001	0.37	0.525	<0.001	0.43
	(c) Hypopharynx	0.566	<0.001	0.39	0.597	<0.001	0.45	0.564	<0.001	0.43
	(d) Lateral pharynx	0.510	<0.001	0.37	0.559	<0.001	0.42	0.569	<0.001	0.40
	(e) Posterior pharynx	0.548	<0.001	0.43	0.553	<0.001	0.41	0.497	<0.001	0.40
	(f) Pyriform fossa	0.639	<0.001	0.42	0.628	<0.001	0.39	0.514	<0.001	0.42
PLMA	(a) Base of tongue	0.469	<0.001	0.45	0.488	<0.001	0.45	0.462	<0.001	0.40
	(b) Distal oropharynx	−0.459	<0.001	0.43	−0.435	<0.001	0.39	−0.409	<0.001	0.39
	(c) Hypopharynx	0.540	<0.001	0.38	0.556	<0.001	0.48	0.529	<0.001	0.42
	(d) Lateral pharynx	0.468	<0.001	0.39	0.488	<0.001	0.41	0.458	<0.001	0.42
	(e) Posterior pharynx	0.413	<0.001	0.36	0.353	<0.001	0.37	0.388	<0.001	0.32
	(f) Pyriform fossa	0.327	0.003	0.50	0.349	<0.001	0.37	0.359	<0.001	0.37

cuff, but found no relationship between directly measured mucosal pressure and OLP. In the earlier study we did not analyse the relationship between directly measured mucosal pressure and OLP by cuff volume, but only by mucosal location and we used a size 5 LMA. We speculate that the relative contribution of the two sealing mechanisms may vary between patients and mask sizes.

Cuff volume, *in vivo* intracuff pressure and calculated mucosal pressure are poor to moderate predictors of directly measured mucosal pressure for both devices. This suggests that these measurements are not useful in determining absolute values for directly measured mucosal pressure even though there is a significant correlation. Our data confirm the findings of a previous study[14] that calculated mucosal pressure is an imprecise method of determining localized directly measured mucosal pressure.

We conclude that the PLMA forms a better seal with the pharynx than the LMA in anaesthetized, paralysed patients, but without an increase in directly measured mucosal pressure. The mechanism of seal for both devices is related to cuff conformity with the pharynx and mucosal pressure. Cuff volume, *in vivo* intracuff pressure and calculated mucosal pressure are imprecise predictors of directly measured mucosal pressure.

References

1 Brimacombe J, Keller C. Laryngeal mask airway size selection in males and females: ease of insertion, oropharyngeal leak pressure, pharyngeal mucosal pressures and anatomical position. *Br J Anaesth* 1999; **82**: 703–7

2 Brimacombe J, Keller C, Giampalmo M, Sparr HJ, Berry A. Direct measurement of mucosal pressures exerted by cuff and non-cuff portions of tracheal tubes with different cuff volumes and head and neck positions. *Br J Anaesth* 1999; **82**: 708–11

3 Brimacombe JR, Brain AIJ, Berry AM. *The Laryngeal Mask Instruction Manual for Anaesthesia* Henley-on-Thames: Intavent Research, 1999

4 Keller C, Brimacombe J, Keller K, Morris R. A comparison of four methods for assessing airway sealing pressure with the laryngeal mask airway in adult patients. *Br J Anaesth* 1999; **82**: 286–7

5 Brimacombe J, Berry A. A proposed fiber-optic scoring system to standardize the assessment of laryngeal mask airway position. *Anesth Analg* 1993; **76**: 457

6 Joshi S, Sciacca RR, Solanki DR, Young WL, Mathru MM. A prospective evaluation of clinical tests for placement of laryngeal mask airways. *Anesthesiology* 1998; **89**: 1141–6

7 Asai T, Howell TK, Koga K, Morris S. Appropriate size and inflation of the laryngeal mask airway. *Br J Anaesth* 1998; **80**: 470–4

8 Sachs L. Der Kolmogoroff–Smirnov-Test fuer die Guete der Anpassung. In: *Angewandte Statistik* Berlin: Springer, 1992; 426–30

9 Rosner B. Hypothesis testing: categorical data. In: *Fundamentals of Biostatistics*. Belmont: Wadsworth Publishing, 1995; 423–6

10 Fleiss JL. Reliability of measurements. In: *The Design and Analysis of Clinical Experiments*. New York: John Wiley, 1986, 2–32

11 Lewis FR, Schlobohm RM, Thomas AN. Prevention of complications from prolonged tracheal intubation. *Am J Surg* 1978; **135**: 452–7

12 Brimacombe J, Keller C, Puehringer F. Pharyngeal mucosal pressure and perfusion. A fiberoptic evaluation of the posterior pharynx in anesthetized adult patients with a modified cuffed oropharyngeal airway. *Anesthesiology* 1999; **91**: 661–5

13 Brimacombe J, Keller C. A comparison of pharyngeal mucosal pressure and airway sealing pressure with the laryngeal mask airway in anesthetized adult patients. *Anesth Analg* 1998; **87**: 1379–82

14 Keller C, Brimacombe J, Benzer A. Calculated versus measured pharyngeal mucosal pressures with the laryngeal mask airway during cuff inflation: an assessment of four locations. *Br J Anaesth* 1999; **82**: 399–401

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Korean hand acupressure reduces postoperative vomiting in children after strabismus surgery

A. Schlager*, M. Boehler and F. Pühringer

Department of Anaesthesia and Intensive Care Medicine, Division of Anaesthesia,
The Leopold-Franzens-University of Innsbruck, Anichstraße 35, A-6020 Innsbruck, Austria
**Corresponding author*

A double-blind, randomized, placebo-controlled study was conducted to investigate the effectiveness of Korean hand acupuncture in preventing postoperative vomiting in children scheduled for strabismus surgery. In one group, acupressure was performed 30 min before induction of anaesthesia by applying an acupressure disc onto the Korean hand acupuncture point K-K9; the disc remained *in situ* for at least 24 h. The second group functioned as placebo group. The treatment groups did not differ with regard to patient characteristics, surgical procedure and anaesthetic administered. In the acupressure group, the incidence of vomiting was significantly lower (20%) than in the placebo group (68%). We conclude that Korean hand acupressure of the acupuncture point K-K9 is an effective method for reducing postoperative vomiting in children after strabismus repair.

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Postoperative vomiting (POV) is a common problem in anaesthesia.[1–3] Several pharmacological and non-pharmacological studies have been performed in search of a means to prevent POV. Well investigated non-pharmacological methods for reducing the incidence of POV are acupuncture and acupressure.[4] Both acupuncture and acupressure of the Chinese acupuncture point Pericard 6 (P6) have been reported to represent an effective non-pharmacological, antiemetic therapy.[5–9]

In contrast to Chinese acupuncture, Korean hand acupuncture is a new method, first developed and described by the Korean physician Dr Yoo.[10] While this method is widely used in Korea, Western medicine has hardly taken any notice of it and little research is being performed in this field.

The Korean hand acupuncture point K-K9 corresponds but is not identical to the Chinese acupuncture point P6, whose antiemetic effect has been ascertained in numerous studies. Therefore, we assumed that K-K9 produces a similar antiemetic effect as P6.

In children undergoing strabismus surgery, POV is one of the most frequent complications.[11] In contrast to pharmacological antiemetic substances, no adverse side effects have been reported for acupressure. Therefore, acupressure could be a useful method for preventing POV, particularly in paediatric patients. However, acupressure of P6 has failed to prevent POV in children in the past.[12]

We investigated the antiemetic effect of acupressure applied onto the Korean hand acupuncture point K-K9 in children undergoing strabismus surgery. This form of acupuncture is painless and thus especially useful in awake children.

Methods

This study was approved by the Ethics Committee of the University of Innsbruck, Austria. Written, informed consent was obtained from the parents. The number of patients required was determined by power analysis (power 0.9). We assumed the incidence of vomiting to be 65% in the control group and 25% in the acupuncture group.

We studied 50 children aged 3–12 yr, ASA physical status I and II, scheduled for strabismus surgery. Children with gastric or intestinal diseases, emesis and vomiting in the week before surgery as well as patients receiving any medical treatment immediately prior to surgery were excluded.

In this double-blind, prospective study each child was allocated randomly to one of the two study groups. Acupressure was performed on the Korean hand acupuncture point K-K9, located on both hands on the middle phalanx of the fourth finger (Fig. 1A).

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Patients in group A underwent acupressure on K-K9. We used a special Korean acupressure disc called 'AB-Bong' (Fig. 1B), which was fixed onto K-K9 using an adhesive tape. Acupressure was performed on K-K9 on both hands for a period of 30 min before induction of anaesthesia and was maintained for at least 24 h.

In group B a tape but no acupressure disc was fixed on both fourth fingers. The children and their parents as well as the anaesthetist and the nursing staff were unaware of the group the children were allocated to. Both acupressure and placebo treatment were performed by the same investigator.

All patients were allowed solid food or clear fluids up to 6 h before anaesthesia. Oral premedication with midazolam 0.4 mg kg^{-1} and atropine 0.02 mg kg^{-1} was administered 1 h before the expected start of anaesthesia. To facilitate a painless placement of an i.v. cannula, ELMA®-5%-Cream (Astra, Austria) was applied to a vein in the left cubita or to the back of the left hand of each child.

Strabismus repair was performed under general anaesthesia. Anaesthesia was induced with i.v. thiopental 5 mg kg^{-1}, rocuronium bromide 0.6 mg kg^{-1} and fentanyl 2 µg kg^{-1}. After intubation, anaesthesia was maintained with 2–3% sevoflurane and nitrous oxide in 33% oxygen under controlled ventilation. Fluid deficit was replaced i.v. by a mixture of three parts of Ringer's lactate solution and two parts 5% dextrose.

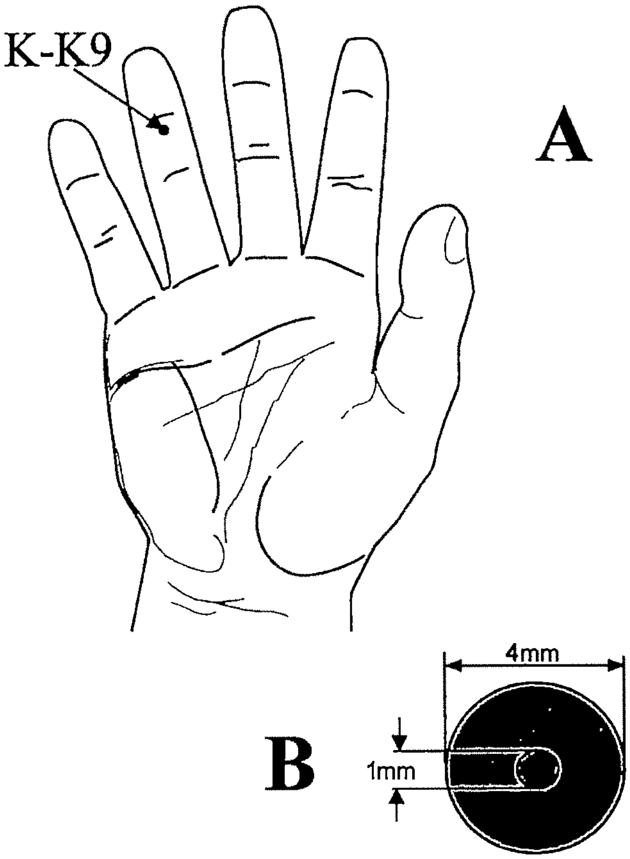

Fig 1 (A) Location of the Korean acupuncture point K-K9. (B) Korean acupressure disc 'AB-Bong' with a central dot (1 mm high and 1 mm in diameter).

At the end of anaesthesia, once the children were fully awake with stable postoperative observations, they were transferred to the ward. Paracetamol suppositories were given for postoperative analgesia and 50 mg dimenhydrinate suppositories for antiemetic rescue therapy.

The incidence of vomiting was recorded by the nursing staff in the recovery room and on the ward. Documentation covered a period of 24 h after starting anaesthesia. All patients remained in the clinic for at least 24 h following surgery.

Statistical analysis

Statistical analysis was performed with SPSS 8.0 (SPSS Inc.®). Fisher's exact test was used to determine the incidence of vomiting, and the unpaired Student's *t*-test to analyse patient characteristics. A *P*-value of less than 0.05 was regarded as statistically significant.

Results

There were no statistical differences between the groups with respect to age, gender, ASA physical status, weight, duration of anaesthesia, and duration or extent of surgery (Table 1).

Compared with the placebo group, the incidence of vomiting in the acupressure group was significantly lower (*P*=0.001). During the first 24 h after surgery, vomiting occurred in five patients (20%; 95% CI: 0.03–0.36) in the acupressure group and 17 patients (68%; 95% CI: 0.48–0.87) in the placebo group. Data on first incidences of vomiting after surgery are shown in Table 2.

Two children receiving acupressure and 10 children in the placebo group required antiemetic rescue therapy.

Table 1 Patient characteristics expressed as numbers or means (SD)

	Acupressure (*n*=25)	**Placebo (*n*=25)**
Age (yr)	6.5 (2.0)	6.1 (1.9)
Sex (M/F)	12/13	12/13
Weight (kg)	22.8 (5.5)	22.9 (8.4)
Anaesthesia duration (min)	69.6 (15.4)	72.2 (17.3)
Surgery duration (min)	47.1 (13.5)	51.1 (16.7)
No. of muscles repaired	2.22 (0.9)	2.52 (0.8)

Table 2 Time of first vomit after surgery. Results expressed in numbers (%) of patients

	0–3 h	**0–6 h**	**0–12 h**	**0–24 h**
Acupressure (*n*=25)	3 (12%)	5 (20%)	5 (20%)	5 (20%)
Placebo (*n*=25)	10 (40%)	14 (56%)	17 (68%)	17 (68%)

Discussion

Korean hand acupuncture is rarely applied in Western medicine. Only a very limited number of studies on the efficiency of Korean hand acupuncture are currently available and no data concerning its antiemetic effect have been published.

The Korean acupuncture point K-K9 is comparable to the well-investigated Chinese acupuncture point P6. Whereas K-K6 is located on the fourth finger, the point P6 is located at the wrist between the tendons of palmaris longus and flexor carpi radialis, 2 Cun proximal from the distal palmar crease. One Cun is equivalent to the width of the patient's thumb across the interphalangeal joint.

Needle acupuncture of P6 effectively reduces postoperative nausea and vomiting.[4,13] However, needle acupuncture of P6 is unpleasant and therefore not useful in routine clinical practice in awake children. The correct timing of acupuncture and acupressure is of great importance. It has been shown that the correct timing of acupuncture further improves the effectiveness of P6 and reduces postoperative vomiting.[14,15] Stimulation of P6 performed before the induction of anaesthesia produced antiemetic effects. Dundee and colleagues[14] found that P6 had no antiemetic effect when opioids had been administered previously. Several investigators were unable to demonstrate an antiemetic effect in paediatric patients when performing acupuncture during general anaesthesia.[4,16–18] We found that, in order to achieve a satisfactory antiemetic effect, stimulation of acupuncture points must be performed before the induction of anaesthesia.[9,15]

In contrast to acupuncture, acupressure is painless, easy to perform and well tolerated by children, as observed in our study. Hence, it seems to be a useful method for preventing POV in paediatric patients.

Nevertheless, the use of acupressure of P6 to prevent postoperative nausea and vomiting has produced inconsistent results. Most investigations in adult patients have reported an effective reduction of POV.[6,7,19,20] However, the method failed in paediatric patients undergoing strabismus surgery.[12] Lewis and colleagues[12] used elastic wrist bands with a plastic stud on the inner aspect of the bands ('sea-bands') for continuous acupressure of P6 and found no difference in the incidence of POV after strabismus surgery compared with a placebo group. In contrast, we found that following acupressure of K-K9, POV in children undergoing strabismus surgery was significantly reduced. An incidence of 72% of POV in children after strabismus surgery without antiemetic therapy, as seen in our study, is consistent with the findings of previous studies.[21–25] Acupressure of K-K9 reduced the incidence of POV to 20%. Because the evaluation of nausea is very difficult in younger children, we did not examine nausea in this study.

The antiemetic effect of K-K9 stimulation by acupressure correlates with that of pharmacological antiemetics administered in various studies to reduce POV in children undergoing strabismus surgery.[22,23,25–27] Pharmacological therapy with drugs such as ondansetron, droperidol and metoclopramide is often associated with side effects such as drowsiness, extrapyramidal symptoms and headache.[28] Unlike these pharmacological antiemetics, acupressure of K-K9 has been found to have no side effects to date.

In conclusion, acupressure of the Korean hand acupuncture point K-K9 is a cheap and effective method for reducing the incidence of POV in children undergoing strabismus surgery. Korean hand acupuncture has been scarcely investigated so far, but its effectiveness has been clearly demonstrated in this study.

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References

1 Korttila K. The study of postoperative nausea and vomiting. *Br J Anaesth* 1992; **69**: 20S–3S

2 Lerman J. Surgical and patient factors involved in postoperative nausea and vomiting. *Br J Anaesth* 1992; **69**: 24S–32S

3 Rowbotham DJ. Current management of postoperative nausea and vomiting. *Br J Anaesth* 1992; **69**: 46S–59S

4 Lee A, Done ML. The use of nonpharmacologic techniques to prevent postoperative nausea and vomiting: a meta-analysis. *Anesth Analg* 1999; **88**: 1362–9

5 al-Sadi M, Newman B, Julious SA. Acupuncture in the prevention of postoperative nausea and vomiting. *Anaesthesia* 1997; **52**: 658–61

6 Allen DL, Kitching AJ, Nagle C. P6 acupressure and nausea and vomiting after gynaecological surgery. *Anaesth Intens Care* 1994; **22**: 691–3

7 Fan CF, Tanhui E, Joshi S, Trivedi S, Hong Y, Shevde K. Acupressure treatment for prevention of postoperative nausea and vomiting. *Anesth Analg* 1997; **84**: 821–5

8 Harmon D, Gardiner J, Harrison R, Kelly A. Acupressure and the prevention of nausea and vomiting after laparoscopy. *Br J Anaesth* 1999; **82**: 387–90

9 Schlager A, Offer T, Baldissera I. Laser stimulation of acupuncture point P6 reduces postoperative vomiting in children undergoing strabismus surgery. *Br J Anaesth* 1998; **81**: 529–32

10 Yoo T.-W. *Koryo Sooji Chim*, 1st edn. Seoul, Korea: Eum Yang Mek Jin, 1977

11 Baines D. Postoperative nausea and vomiting in children. *Paediatr Anaesth* 1996; **6**: 7–14

12 Lewis IH, Pryn SJ, Reynolds PI, Pandit UA, Wilton NC. Effect of P6 acupressure on postoperative vomiting in children undergoing outpatient strabismus correction. *Br J Anaesth* 1991; **67**: 73–8

13 Dundee JW, Ghaly RG, Bill KM, Chestnutt WN, Fitzpatrick KT, Lynas AG. Effect of stimulation of the P6 antiemetic point on postoperative nausea and vomiting. *Br J Anaesth* 1989; **63**: 612–8

14 Dundee JW, Milligan KR, McKay AC. Influence of intraoperative acupuncture and droperidol on postoperative emesis. *Br J Anaesthesia* 1988; **61**: 116P–7P

15 Dundee JW, Ghaly RG. Does the timing of P6 acupuncture influence its efficacy as a postoperative antiemetic. *Br J Anaesthesia* 1989; **63**: 630P

16 Schwager KL, Baines DB, Meyer RJ. Acupuncture and postoperative vomiting in day-stay paediatric patients. *Anaesth Intens Care* 1996; **24**: 674–7

17 Yentis SM, Bissonnette B. P6 acupuncture and postoperative vomiting after tonsillectomy in children. *Br J Anaesth* 1991; **67**: 779–80

18 Yentis SM, Bissonnette B. Ineffectiveness of acupuncture and droperidol in preventing vomiting following strabismus repair in children *Can J Anaesth* 1992; **39**: 151–4

19 Dundee JW, Yang J. Prolongation of the antiemetic action of P6 acupuncture by acupressure in patients having cancer chemotherapy. *J R Soc Med* 1990; **83**: 360–2

20 Gieron C, Wieland B, von der Laage D, Tolksdorf W. Acupressure in the prevention of postoperative nausea and vomiting. *Anaesthesist* 1993; **42**: 221–6

21 Karlsson E, Larsson LE, Nilsson K. The effects of prophylactic dixyrazine on postoperative vomiting after two different anaesthetic methods for squint surgery in children. *Acta Anaesthesiol Scand* 1993; **37**: 45–8

22 Lin DM, Furst SR, Rodarte A. A double-blinded comparison of metoclopramide and droperidol for prevention of emesis following strabismus surgery. *Anesthesiology* 1992; **76**: 357–61

23 Munro HM, Riegger LQ, Reynolds PI, Wilton NC, Lewis IH. Comparison of the analgesic and emetic properties of ketorolac and morphine for paediatric outpatient strabismus surgery. *Br J Anaesth* 1994; **72**: 624–8

24 Nicolson SC, Kaya KM, Betts EK. The effect of preoperative oral droperidol on the incidence of postoperative emesis after paediatric strabismus surgery. *Can J Anaesth* 1988; **35**: 364–7

25 Rose JB, Martin TM, Corddry DH, Zagnoev M, Kettrick RG. Ondansetron reduces the incidence and severity of poststrabismus repair vomiting in children. *Anesth Analg* 1994; **79**: 486–9

26 Fujii Y, Toyooka H, Tanaka H. Antiemetic efficacy of granisetron and metoclopramide in children undergoing ophthalmic or ENT surgery. *Can J Anaesth* 1996; **43**: 1095–9

27 Vener DF, Carr AS, Sikich N, Bissonnette B, Lerman J. Dimenhydrinate decreases vomiting after strabismus surgery in children. *Anesth Analg* 1996; **82**: 728–31

28 Domino KB, Anderson EA, Polissar NL, Posner KL. Comparative efficacy and safety of ondansetron, droperidol, and metoclopramide for preventing postoperative nausea and vomiting: a meta-analysis. *Anesth Analg* 1999; **88**: 1370–9

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Building a large-scale perioperative anaesthesia outcome-tracking database: methodology, implementation, and experiences from one provider within the German quality project

U. Bothner[1 2]*, M. Georgieff[2] and B. Schwilk[2]

[1]*Department of Anaesthesiology and Intensive Care Medicine, University of Ulm, D-89070 Ulm, Germany.*
[2]*Department of Medical Informatics, University of Utah, Salt Lake City, Utah 84132, USA*
**Corresponding author*

The German Society of Anaesthesiology and Intensive Care Medicine evaluates voluntary, standardized, everyday, perioperative anaesthesia outcome measures. A standard minimal data set is collected for national benchmarking. This article reviews the implementation of a data acquisition system in one academic centre that has participated in this long-term nationwide project since its initiation in 1992. The population studied comprised 96 107 patients up to 1997. The overall incidence of anaesthesia-related incidents, events and complications (IEC) was 22%. Results are presented and discussed for 63 different IEC, seven functional system categories and five severity grades. The proposed methodology, using computer-readable records, was suitable for comprehensive and detailed outcome documentation. However, an extensive data validation system was necessary. IEC reporting results were largely dependent on the documentation culture. The future of outcome tracking in routine anaesthesia may lie in multicentre comparisons with multivariate-adjusted risk and comorbidity data from each provider's integrated information system.

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The value of performance information and the need for quality assessment in hospital care are generally appreciated.[1] Specifically for the specialty of anaesthesia, there is increasing interest by providers, purchasers, politicians and patients in outcome analysis.[2]

The German Society of Anaesthesiology and Intensive Care Medicine (Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI)) launched a study[3] following the introduction of quality assurance and cost-containment regulations imposed by German health-care law. The aim of the project was to implement and evaluate a methodology for the standardized, long-term reporting of everyday anaesthesia outcome measures. Routine assessment of anaesthesia-related incidents, events and complications (IEC) was recommended for each patient and every anaesthetic procedure performed. A standard minimal data set is collected for national benchmark comparisons.[4] Our department has been one of the pilot centres in this nationwide project.

This article attempts to (i) describe the methodology of the project concerning the immediate perioperative timeframe of anaesthesia care, and (ii) review the implementation and results of a routine data acquisition system that includes data collection, validation and staff education in one academic anaesthesia provider institution.

Methods

Presumptions

According to the German health-care reform law, in effect since 1989, clinical institutions have to measure quality in such a way that comparisons with other hospitals are possible. As an immediate response, the DGAI developed a project outline. Definitions were set by the use of an expert consensus approach. Cooper's concept of 'anaesthetic mishaps' and 'near-miss incidents'[5] served as a starting model. A prototype of the assessment methodology was tested over a 6-month period in nine clinics representing different structure levels of anaesthesiology care.[6] It was assumed that the quality of anaesthesia is never measurable in an absolute manner, and that inclusion of all anaesthetic department activity would not be economically viable. Rather, a three-step process was proposed: (i) intra-institutional quality tracking with online or periodic retrospective comparisons; (ii) voluntary inter-institutional comparisons

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between anaesthesia providers with equivalent sizes and levels of care; and (iii) periodic retrospective multicentre comparisons between representative anaesthesia providers from a national database through proposed benchmark standards. Failure to meet benchmarks was intended to trigger further quality improvement investigations in the particular institution.[3] After testing of the prototype until 1992, the project has been open to all German clinical anaesthesia providers on a voluntary basis during a field evaluation phase. Participation in the project implied several requirements: the provider employs (i) one uniform routine documentation tool for all patients and all anaesthetists throughout the institution, (ii) one integrated record set for individual patient care documentation, archiving and quality assessment purposes, to avoid inconsistencies and minimize documentation workload, and (iii) a standard data set from each procedure that can be submitted to a national database. Outcome information was to be handled confidentially and anonymously, to be detachable from the record set by the end of the perioperative period, and not to be part of the definite archived patient record.

Quality measurement dimensions

The recommended outcome measurements of the whole project have three dimensions:

(i) perioperative reporting on IEC occurring during anaesthesia;
(ii) postoperative reporting on IEC occurring after anaesthesia;
(iii) postoperative patient satisfaction inquiry.

Perioperative IEC, according to Donabedian's triad,[1] represent quality-of-process measures of the immediate anaesthesia care process. Postoperative variables represent the quality of outcome. Methodology and results for quality of outcome have been described in detail elsewhere for a specific study period at our hospital[7] and are beyond the scope of this article.

Standard data set

The standard data set was designed to reflect several key issues as to which patient (e.g. demographic and administrative data, risk factors, pre-existing disease, admitting surgical department) experiences which problems during what procedure (e.g. the kind and duration of anaesthesia and operation). The DGAI recommended the following definition of anaesthesia-related IEC:[3]

(i) IEC occur during the anaesthetist's perioperative responsibility, i.e. from the induction of anaesthesia until discharge of the patient to the ward or intensive care unit (ICU), either from the postanaesthesia care unit (PACU) or directly from the operating theatre.
(ii) IEC lead to intervention by the anaesthetist.
(iii) IEC have or could have caused morbidity or mortality if the anaesthetist had not intervened.

All three conditions have to be fulfilled. By definition, it does not matter if the incident occurred by chance, was caused by the patient's preoperative condition, or was a consequence of inadequate treatment by the responsible physician. Usually, physicians are able to assess IEC with standard clinical methods. The DGAI has defined 63 kinds of IEC (Table 2) and five ascending grades of severity as follows:

(i) IEC without any impact on postoperative care—no additional postoperative care necessary (including near incidents).
(ii) IEC clinically important only for care in the PACU—no impact on transfer to the ward.
(iii) IEC clinically relevant for postoperative care—prolonged stay in the PACU or particular observation on the ward is clearly necessary.
(iv) IEC clinically important for postoperative care—problem cannot be solved satisfactorily in the PACU, and transfer to intermediate care unit or ICU necessary.
(v) IEC presumably severe, with permanent damage or death.

Acquisition of data

With the advent of our participation in the DGAI project in 1991, we decided to implement a uniform, paper-based, yet computer-readable anaesthesia record system for every monitored anaesthetic procedure. The system was developed according to ergonomic principles[8] and was available at any anaesthetic location throughout the hospital. Each record set contained three pages:

(1) Preoperative evaluation with patient details, medical history, laboratory and pathophysiology findings, American Society of Anesthesiologists (ASA) classification of physical status, and surgical specialty.
(2) Intraoperative documentation of anaesthesia care, surgical procedure, monitoring techniques and notes on transfer.
(3) Postoperative course in the PACU, timing of operation and anaesthesia, length of stay in the PACU, type and severity of IEC, and the patient's transfer destination.

The documented course of vital signs, the type and dosage of anaesthetics and the administration of other drugs in the operating theatre and PACU were not to be stored in the database. Before storing data in the database, every record set was validated in four ways and was corrected if necessary (Fig. 1).

(i) The consultant anaesthetist in charge at the point of care reviewed each record set for accuracy and completeness, usually at the end of the daily operating list.
(ii) Documentation clerks checked each record set for technical errors to guarantee proper scanning of the paper.

Table 1 Patient population: type of anaesthesia and main surgical procedure

	n	(Total %)
General anaesthesia		
Endotracheal intubation	64050	(66.6)
Laryngeal or face mask	8406	(8.7)
Regional anaesthesia		
Spinal	6664	(6.9)
Epidural	4556	(4.7)
Major nerve block	2372	(2.5)
Other anaesthesia care		
Epidural and general anaesthesia (planned)	2959	(3.1)
Monitored anaesthesia care (standby)	1845	(1.9)
Not otherwise specified (intravenous anaesthesia with spontaneous respiration, conscious sedation, etc.)	5255	(5.5)
Surgery		
Peripheral	33892	(35.3)
Genito-urinary	13214	(13.7)
Head or neck	22271	(23.2)
Laparoscopy	10587	(11.0)
Laparotomy	4555	(4.7)
Obstetric	3375	(3.5)
Caesarean section	1949	(2.0)
Spine	649	(0.7)
Brain	105	(0.1)
Thoracotomy	1693	(1.8)
Cardiac	3817	(4.0)
Totals	96107	

(iii) Rules implemented in the database system checked each record set for completeness, consistency and plausibility.

(iv) If there were any doubts in the second or third step of the validating system, the anaesthetists in charge of the documentation work group (B.S. or U.B.) were asked for assistance. If necessary, the anaesthetist who had performed the anaesthesia was asked to complete the data.

During a pilot phase from September 1991 to June 1992, clinical and documentation staff were trained to use the documentation system and to classify IEC. Written guidelines and educational meetings supported the staff education efforts. During the pilot phase, we conducted time studies and staff surveys. After implementation of the IEC methodology, our regular documentation activity began in July 1992.

Hospital, patient and anaesthesia characteristics

The data were collected from a tertiary university teaching centre completing about 18 000 anaesthetics per year. The case mix covered patients from an urban and a rural area, as the university surgical clinics function both as city hospitals

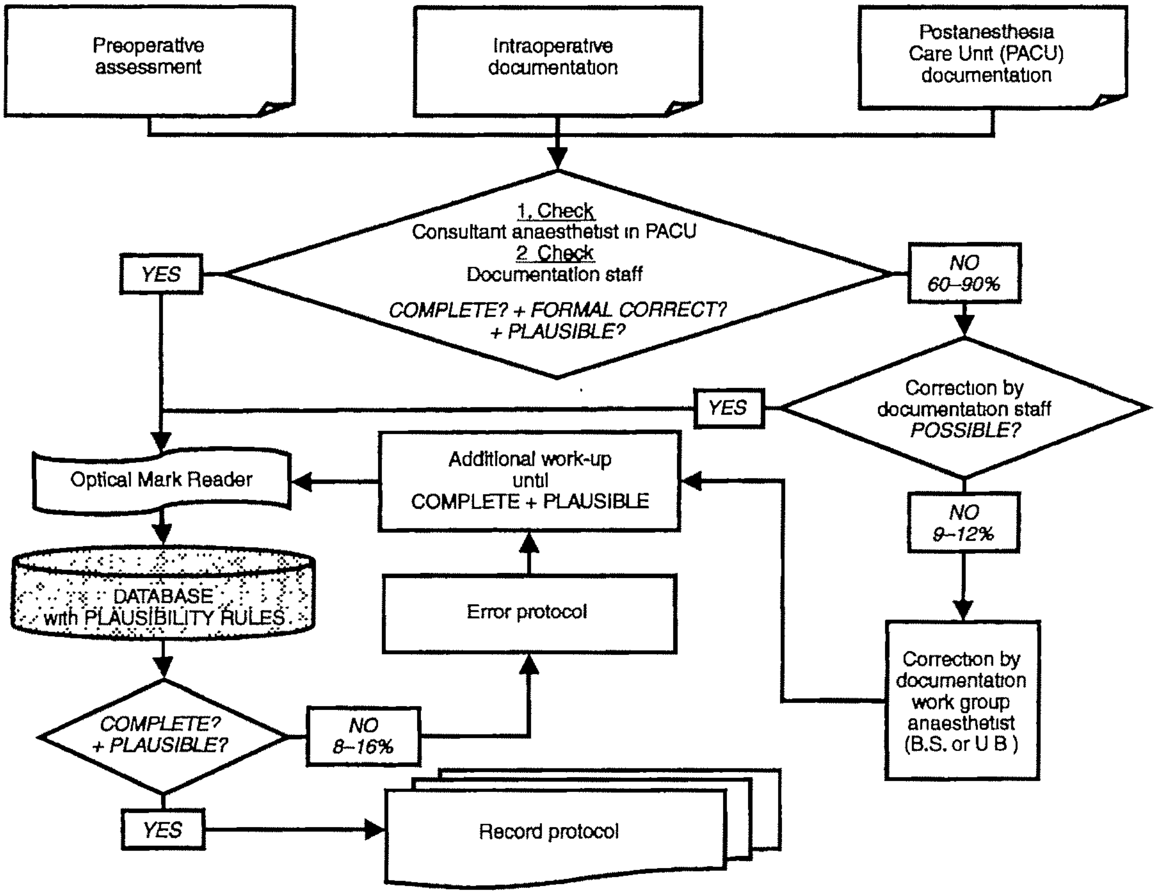
Preoperative assessment
Intraoperative documentation
Postanesthesia Care Unit (PACU) documentation
1. Check
Consultant anaesthetist in PACU
2. Check
Documentation staff
COMPLETE? + FORMAL CORRECT? + PLAUSIBLE?
YES
NO 60–90%
Correction by documentation staff POSSIBLE?
YES
NO 9–12%
Optical Mark Reader
Additional work-up until COMPLETE + PLAUSIBLE
Correction by documentation work group anaesthetist (B.S. or U.B.)
DATABASE with PLAUSIBILITY RULES
Error protocol
COMPLETE? + PLAUSIBLE?
NO 8–16%
YES
Record protocol

Fig 1 Workflow scheme of data acquisition, validation, correction, and storage to the database

Table 2 Frequency and severity of IEC. Notation of more than one IEC per anaesthesia is possible

	IEC severity grade						
	I	II	III	IV	V	**Total *n***	**(Total %)**
Airway and respiratory system							
Disconnection	45	3	–	–	–	48	(0.05)
Obstructed tube	43	15	5	1	–	64	(0.1)
Accidental extubation	42	28	4	–	–	74	(0.1)
Unexpected difficult intubation (more than three intubation attempts or intubation by a second physician)	440	230	50	14	–	734	(0.8)
Intubation not possible	14	16	6	2	–	38	(0.04)
Intubation failure (second intubation attempt)	102	24	5	2	–	133	(0.1)
One-sided intubation (repositioning after tube fixation)	85	22	4	–	1	112	(0.1)
Reintubation	72	21	25	32	–	150	(0.2)
Laryngospasm	52	87	30	4	–	173	(0.2)
Bronchospasm	251	350	123	40	–	769	(0.8)
Aspiration	5	12	21	28	1	67	(0.1)
Hypoventilation, hypoxaemia	185	244	233	153	9	824	(0.9)
Pulmonary oedema	4	10	17	17	1	49	(0.05)
Other respiratory problems	245	281	191	107	4	828	(0.9)
Cardiovascular circulation							
Hypotension	4011	2129	467	197	20	6824	(7.1)
Hypertension	1350	1190	272	19	–	2831	(2.9)
Arrhythmia	856	512	254	99	8	1729	(1.8)
Tachycardia	499	481	249	77	4	1310	(1.4)
Bradycardia	1522	590	130	32	3	2277	(2.4)
Hypovolaemia	121	271	186	119	20	717	(0.7)
Heart failure	1	5	23	65	12	106	(0.1)
Pulmonary embolism	4	2	2	8	2	18	(0.02)
Cardiac arrest	10	14	15	40	48	127	(0.1)
Myocardial infarction	2	2	1	6	1	12	(0.01)
Other cardiovascular problem	74	84	82	53	13	306	(0.3)
Systemic reactions							
Nausea or vomiting	1203	982	104	3	–	2292	(2.4)
Hypersensitivity, anaphylaxis	89	69	28	15	–	201	(0.2)
Shivering	842	637	20	–	–	1499	(1.6)
Hypothermia	22	74	152	38	1	287	(0.3)
Malignant hyperthermia	–	1	3	–	–	4	(0.00)
Transfusion reaction	1	2	5	1	–	9	(0.01)
Oliguria, anuria, acute kidney failure	20	42	18	14	2	96	(0.1)
Other systemic reaction	169	155	75	22	1	422	(0.4)
Laboratory findings							
Anaemia	86	222	132	41	4	485	(0.5)
Acid–base status disorder	15	79	50	42	2	188	(0.2)
Electrolyte disorder	118	215	88	18	2	441	(0.5)
Hyper-/hypoglycaemia	19	44	52	10	–	125	(0.1)
Other	7	46	24	23	2	102	(0.1)
Central nervous system							
Central anticholinergic syndrome	3	8	11	1	–	23	(0.02)
Ischaemia	–	–	1	4	–	5	(0.01)
Seizure	3	3	5	3	–	14	(0.01)
Other central neurological problem	29	33	47	10	2	121	(0.1)
Medical equipment							
Anaesthesia machine, ventilator	317	33	3	–	–	353	(0.4)
ECG monitoring	131	12	3	–	–	146	(0.2)
Automated blood pressure monitoring	190	23	6	–	–	219	(0.2)
External pacemaker	–	1	–	–	–	1	(0.00)
Defibrillator	2	1	–	–	–	3	(0.00)
Oximetry	119	14	2	1	–	136	(0.1)
Intubation equipment	13	1	–	–	–	14	(0.01)
Drug application (infusion systems or pumps)	20	5	3	–	–	28	(0.03)
Other equipment problem	220	46	7	1	–	274	(0.3)
Lesions							
Difficult puncture in regional anaesthesia (more than three puncture attempts or puncture by a second physician)	416	145	27	–	–	588	(0.6)
Difficult puncture in vessels (more than three puncture attempts or puncture by a second physician)	603	186	31	4	–	824	(0.9)
Teeth	44	8	10	–	–	62	(0.1)
Vessels	7	1	2	–	–	10	(0.01)
Muscle, smooth tissue	12	10	1	1	1	25	(0.03)
Skin	14	4	2	–	–	20	(0.02)
Airway	1	–	2	–	–	3	(0.00)

	IEC severity grade						
	I	II	III	IV	V	Total *n*	(Total %)
Eyes	–	–	1	–	–	1	(0.00)
Epistaxis	19	8	5	1	–	33	(0.03)
Pneumo-/haemothorax	–	–	3	2	–	5	(0.01)
Nerves	2	1	–	–	–	3	(0.00)
Other lesion	33	23	18	2	–	76	(0.1)
Total *n*	14824	9757	3341	1372	164	29458	
(Total %)	(15.4)	(10.2)	(3.5)	(1.4)	(0.2)	(30.7)	

and tertiary referral centres. Our department has a strict policy for the guideline-driven performance of anaesthesia according to our institutional practice recommendation.[9] The current study was approved by the Institutional Review Board (Health Sciences) of the University of Utah.

Results

The results presented here refer to validated record sets of 96 107 anaesthetic procedures carried out between July 1992 and November 1997. Patient sex was evenly distributed. ASA physical status score and urgency of the procedures are shown in Figure 2. Types of anaesthesia and surgical operation are listed in Table 1. All outcomes are listed in Table 2 for the complete IEC assessment scheme.

Overall, the proportion of procedures with any IEC was 22.0%. The proportion of procedures with a maximum IEC grade of I was 11.2%; II, 7.4%; III, 2.4%; IV, 0.9%; and V, 0.1%. Incidences of IEC with respect to risk factors are shown in Figures 3–5.

The workflow studies in the pilot phase of implementation revealed that 60–90% of all records needed correction (mostly because the marks by the anaesthetist were unsuitable for scanning) before being scanned by the optical mark reader. Additional validation efforts were necessary before the data could be stored in the database (Fig. 1). Time studies showed that the documentation personnel spent 2 min on each record and the clinicians 4 min. A survey of the 110 anaesthetists in our department determined that there should be no duplication of documentation for patient care; that for outcome reporting the preanaesthesia assessment record should be structured according to organ and functional systems and reflect increasing severity of risk features; and that there should be ample space for handwritten remarks on the record.

Discussion

This article describes a routine system of measuring, collecting, validating and analysing outcome data for perioperative anaesthesia. Coding and grading of IEC was accomplished with the methodology recommended by the DGAI.

Definitions of anaesthesia outcome

There has been a consistent lack of agreement on how to appraise adverse events, adverse outcomes and quality in anaesthesia. Various countries and research groups differ widely in their criteria for reporting events: some restrict reporting to events with legal or disciplinary consequences;[16] others report mortality or major morbidity only.[11 12] Also, there is an inconsistent definition of the perioperative period: some reports cover the time from induction of anaesthesia until discharge from the recovery unit[15] and others the time from the beginning of anaesthesia until 24 h postoperatively,[11] or an even longer period.[12 14 15] Furthermore, the method of data acquisition varies from voluntary individual reporting of critical incidents[15] to prospective studies covering all anaesthetics during a certain period for one[16] or several[14] departments.

Instead of reporting particular findings in particular patient groups, the IEC definitions were designed to document everyday problems and their clinical impact on the entire patient population. Documentation was to continue during that precisely specified episode of care when the anaesthetist is completely and solely responsible for the patient, i.e. the induction and maintenance of anaesthesia in the operating theatre and through recovery and transfer from the PACU.

Accurate definitions of criteria for adverse events are difficult to set. Many problems cannot be measured by technical instrumentation (e.g. intubation problems, difficult punctures). Even if threshold values are measurable, rules about them may vary substantially in a complex clinical context. For example, a decrease in systolic arterial blood pressure from 130 to 80 mm Hg may or may not be classified as hypotension depending on whether it occurs in an old patient with cardiovascular disease or in a young healthy woman. For automated incident reporting, the defining of criteria may never reach the sophistication of the caring clinician.[17] Therefore, the severity grading of an IEC is not defined by numerical values but rather by its clinical impact on the immediate and postoperative course.

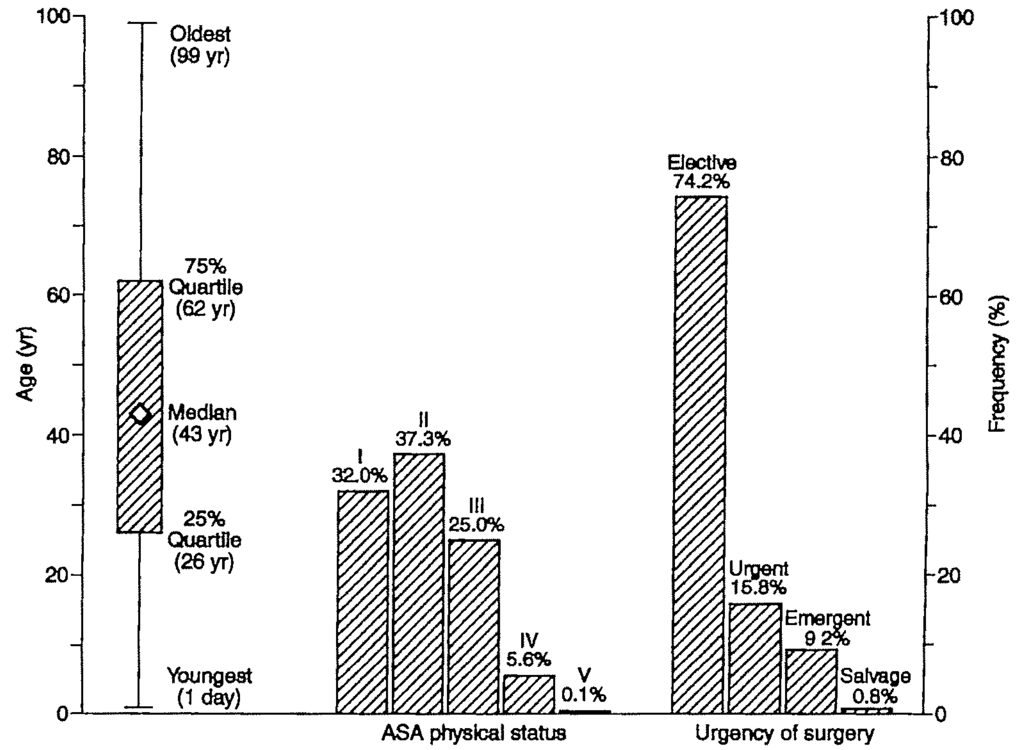

Fig 2 Risk features of patient population (n=96 107). Distribution of patient age is shown in the box-whisker plot. Distributions of ASA physical status score and urgency of surgical intervention (urgent=24 h preparation time; emergent=2 h; salvage=immediate life-saving intervention (e.g. emergency Caesarean section, shock, ruptured aortal aneurysm)) are shown in the frequency histograms

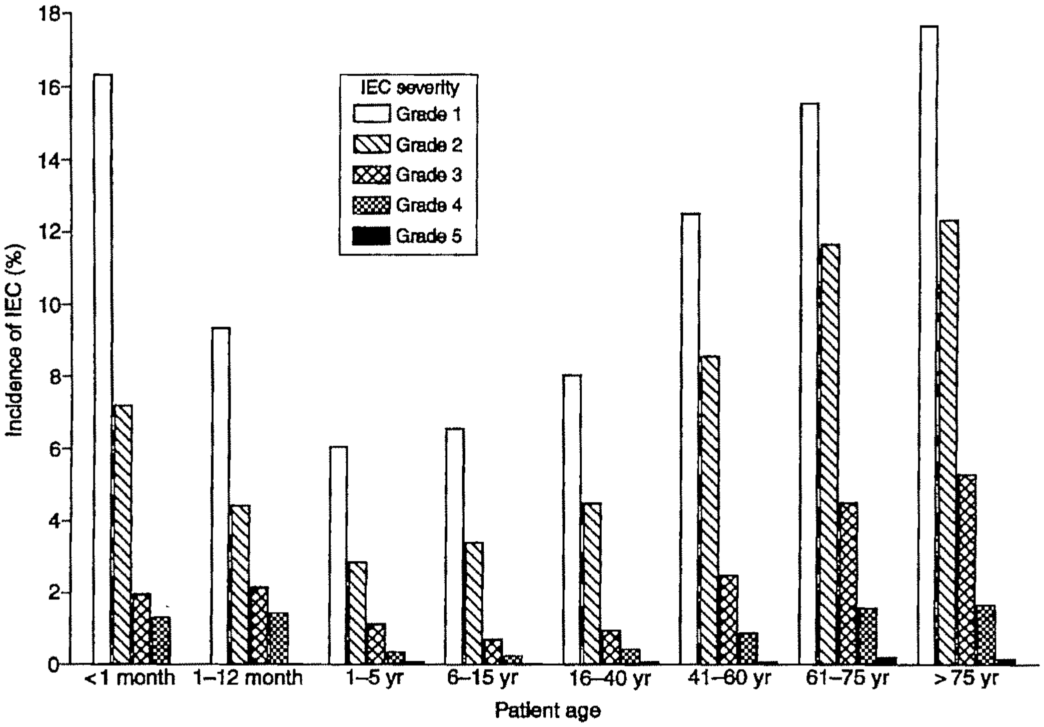

Fig 3 Incidence of the maximum severity grade of anaesthesia-related IEC per anaesthetic procedure with respect to patient age (may include several different functional IEC with equal or less severe grades)

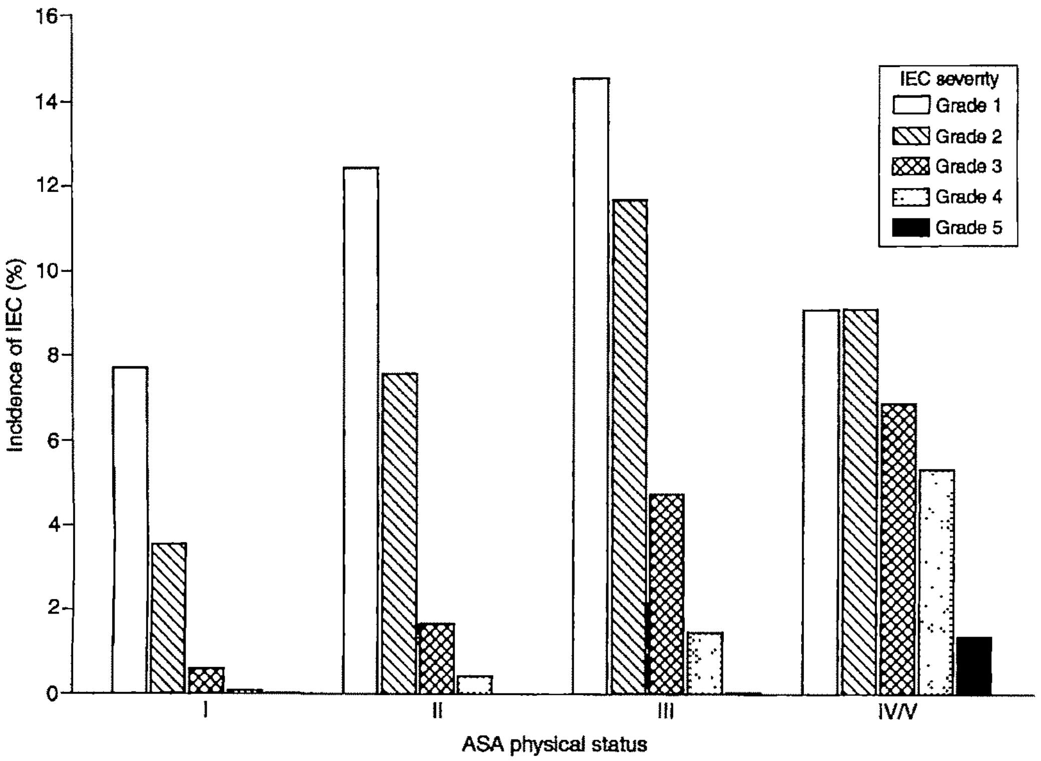

Fig 4 Incidence of the maximum severity grade of anaesthesia-related IEC per anaesthetic procedure with respect to ASA physical status score (may include several different functional IEC with equal or less severe grades)

The DGAI defined no criteria to determine what is causally responsible for an event (e.g. the anaesthesia or the surgical procedure). Most of the time, particularly in critical situations, this is hard to determine because interactions are abundant and complex. Even if it were possible to make them, such distinctions would offer no gain in quality information. In addition, it could be a common reason for doctors to refrain from documenting certain incidents for fear of being blamed.

International incidence comparisons

The overall incidence of IEC in our population, 22.0%, was higher than in other German reports using the same definitions.[18 19] An overall incidence of 8% was shown to be low and inaccurate when the records were reviewed afterwards.[22] Reported complication rates of 0.05%[10] may be explained only if restricted inclusion criteria are considered (e.g. incidents with potential medicolegal consequences). Cooper *et al.*[15] found a rate of adverse events of 18%. These events were called 'recovery room impact events' and their definition is very similar to that of our IEC of grade II or above. The corresponding rate in our population was 10.7%. The incidence of 'moderate, serious or catastrophic sequelae' in Cooper's study was between 2.7 and 3.6%, compared with 3.3% in our study. However, our patient population, in contrast to Cooper's, included patients transferred to an ICU immediately after surgery (see definition of grade IV). Cohen *et al.*[16] found a rate of overall events of 25–32% and a rate of 'major postoperative complications' of 0.4%. Forrest *et al.*[21] used a definition similar to ours and also five grades of severity. They found at least one 'severe adverse outcome' in 4.9% of the study population. The 'total complication rate' in the Gothenburg study of perioperative risk[22] was 30%. However, it covered a longer postoperative period. Generally, the rate of severe adverse events is difficult to compare because of different severity grading systems and criteria for inclusion in studies. Pedersen *et al.*[23] reported a complication rate of 3.6% when they included various severe cardiopulmonary events that were quite similar to our IEC of grade III and above

In terms of specific events, Cohen *et al.* found more arrhythmia.[14 16] Our incidences of severe cardiovascular events (hypotension, hypertension, tachycardia and arrhythmia) were slightly below the frequencies reported by Forrest *et al.*[21] Unexpected difficult intubation is reported to occur with a frequency of about 1%,[13 16] which is similar to our result. Reporting for bronchospasm was also similar. In our population, the incidence of hypoxaemia was higher (0.9 *vs* 0.4%) than in the report by Cooper *et al.*[13] The study from Gothenburg[24] revealed a lower incidence of respiratory events.

Other events play a minor role in our population, especially if we focus on severity grades above II. Fewer than 25% of all severe IEC did not involve the cardiovas-

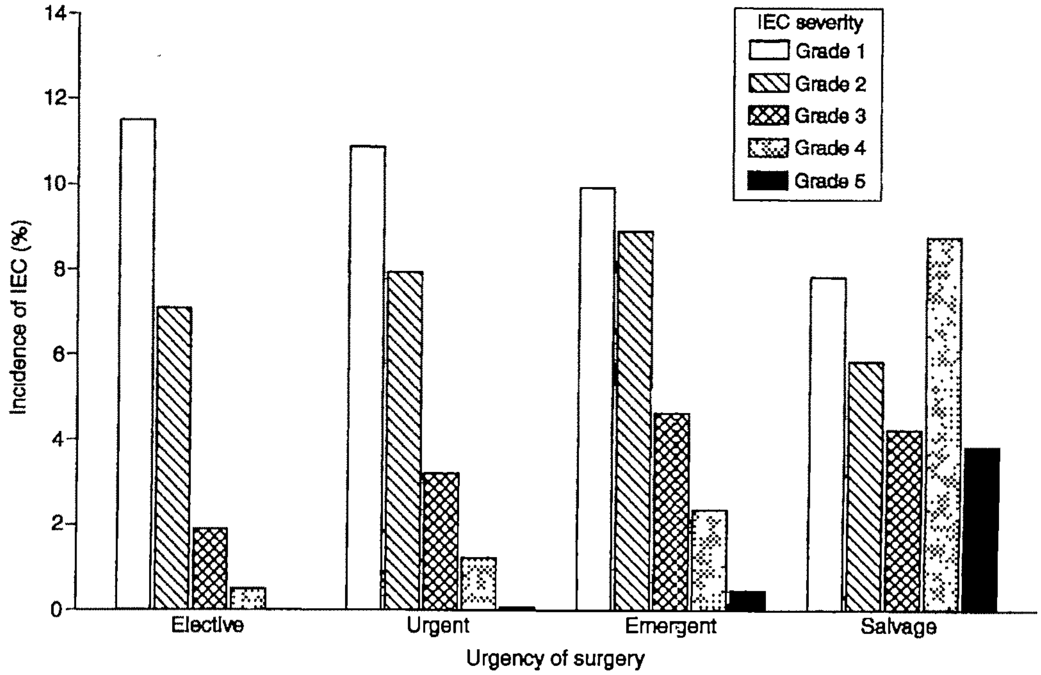

Fig 5 Incidence of the maximum severity grade of anaesthesia-related IEC per anaesthetic procedure with respect to urgency of surgery (may include several different functional IEC with equal or less severe grades). For definition of urgency see legend to Figure 2.

cular or respiratory system. For example, severe equipment IEC were rare (0.53%). Cooper *et al.* found that equipment was involved in only 4% of 'avoidable' severe incidents.[25] Their investigation, however, was carried out more than 10 years ago and technical standards and system checks may have improved in the meantime. Although 'incidence' is clearly defined as the new occurrence of an event, this may be difficult to determine in practice. Consider, for example, a patient with a recent myocardial infarction undergoing a short emergency procedure. This procedure may be uneventful but the patient would be subject to close observation in the PACU for a prolonged time and then be transferred to an intermediate care unit or ICU for further cardiac monitoring. We suspect that many anaesthetists will document this situation incorrectly. This may explain the relatively high frequencies of low severity grades with intrinsically severe conditions. 'Near' incidents, however, are included in the methodology.

Our incidence of disconnection, nausea and vomiting, and disorders of laboratory parameters was probably too low. In a recent study we found that the long-term variance of IEC incidences with a low severity grade are heavily dependent on discipline in staff documentation, and may therefore not be reliable indicators for quality comparisons.[26]

General problems in incident reporting

Many aspects will influence reporting. If, in addition to the usual anaesthesia record, any further reporting activity is required (e.g. finding and filling in a particular report form), there is a tendency among anaesthetists to report only the most severe events.[27] For this reason, we have installed a record-keeping system with an integrated module for incident reporting. To prevent major bias, the reporting of incidents should be influenced neither by the anaesthetists' fears nor by their individual opinions about what is worth documenting. Our department has kept a strict policy of confidentiality. Clearly, there is a trade-off between clinical education and departmental supervision capabilities for the validity of quality data.

Before starting the project, our department commissioned a documentation working group. This group instructed all medical staff in our department. Training in handling the record and classifying and grading IEC were carried out by the provision of formal guidelines and educational meetings. From then on, new staff members were tutored at regular intervals. Critical incidents were discussed in daily meetings. We learned that IEC reporting is highly sensitive to positive and negative educational effects on documentation discipline and that anaesthesia providers have to know the sources of influence and to be aware of the possibility of manipulating the system.[26]

We have learned that leading a project of this size is no task for those who are easily discouraged. It requires determination and enthusiasm, patience and persistence, complete support from the department, and considerable resources. This is necessary because motivating staff in what will lead to a substantial cultural change in documentation and practice is a tough barrier,[28] particularly if the benefit is indirect. Detecting and reducing unreasonable variation in practice, however, should reduce costs and provide a predictable quality of patient care, which in turn helps to make a clinical facility with its employees more competitive.[29] A good argument in discussions about the project has always been that it might be better to contribute proactively to one's own quality project than to wait until somebody else imposes their regulations. Later, during the course of the project, we experienced that passing coded information about the occurrence of IEC was an excellent way of streamlining information transfer in hand-over situations, and thus it aided decision-making even in individual cases (e.g. specific preparations for repeated anaesthesia if previous IEC are reported during preoperative assessment).

Another barrier is the need to convince medical professionals of the necessity of encoding information. Free text data is worthless for automated decision support and scientific work-up (e.g. statistics, epidemiology, economic analyses). Therefore, space for handwritten remarks, although ranked highly on the staff request survey, is limited on our anaesthesia record. Our preanaesthesia record, however, allows detailed coding of historical, clinical, laboratory and physiology data organized within functional systems and stratified according to severity. If information is stripped to the bare facts, the record is processed faster and more accurately, especially in hand-over situations.

Educating staff members to check optical mark-reading protocols properly may appear to be a simple task, but it is hard to achieve. In an initial workflow study, we found that most of the errors were of a technical nature related to these protocols.[30] Therefore, we have relied on an integrated validating system involving point-of-care clinicians, dedicated documentation physicians and trained data clerks.

The technology employed represents devices commercially available at the time (1991) the project started: one optical mark reader, a relational database running on a single workstation, and batch processing of the paper forms, with considerable delay in the updating of information. Beginning in October 1997, we have introduced a new real-time system with workstations and printers in all pre-anaesthesia offices, several optical mark readers and printers in all PACUs, and a fully computerized patient record. It is still possible to document an anaesthetic completely on paper and to feed the data into the system later, because we have many anaesthetic locations that have no network connection and may not have one in the near future.

General critique of the IEC system

Comprehensive quality assurance in anaesthesia is not accomplished with external benchmark comparisons alone. In addition, there has to be an internal auditing and supervising system within each department which is concerned with the specific errors or mistakes of the individual care-provider and the clinical system environment (e.g. wrong drug or equipment usage). These occurrences are usually rare and are difficult to evaluate with standard statistics. The IEC system is not targeted at the thorough evaluation of rare, stochastic errors. The main purpose of the IEC system is to evaluate common problems in day-to-day anaesthesia patient care.

Unfortunately, there is no tradition and no clear move in Germany towards the national reporting and discussion of 'stochastic' anaesthesia incidents, such as the Confidential Enquiry into Perioperative Death (CEPOD)[31] in the UK or the Australian Incident Monitoring Study.[15] An ideal quality assurance system for anaesthesia would have to include at least three components: a CEPOD-style reporting system; a benchmarking system operating on a state or national scale, and a culture of maintaining and animating local quality peer review groups.

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References

1 Donabedian A. The quality of care. How can it be assessed? *JAMA* 1988; **260**: 1743–8

2 Abenstein JP, Warner MA. Anesthesia providers, patient outcomes, and costs. *Anesth Analg* 1996; **82**: 1273–83

3 Deutsche Gesellschaft fur Anasthesiologie und Intensivmedizin. Massnahmen zur Qualitätssicherung von Anasthesieverfahren. *Anaesth Intensivmed* 1992; **33**: 78–83

4 Deutsche Gesellschaft fur Anasthesiologie und Intensivmedizin. Kerndatensatz Qualitatssicherung in der Anästhesie. *Anaesth Intensivmed* 1993; **34**: 331–6

5 Cooper JB, Newbower RS, Long CD, McPeek B. Preventable anesthethic mishaps. *Anesthesiology* 1978; **49**: 399–406

6 Kersting T Qualitatssicherung in der Anasthesiologie—Verfahrensentwicklung und Verfahrenserprobung. *Anaesth Intensivmed* 1989; **30**: 343–7

7 Bothner U, Schwilk B, Steffen P, Eberhart LH, Becker U, Georgieff M. Perioperative Anästhesieverlaufsbeobachtungen, postanästhesiologische Visite und Befragung zur Patientenzufriedenheit. *Anaesthesiol Intensivmed Notfallmed Schmerzther* 1996; **31**: 608–14

8 Friesdorf W, Konichezky S, Gross Alltag F, Schwilk B Ergonomics applied to anaesthesia record keeping. *Int J Clin Monit Comput* 1993; **10**: 251–9

9 Georgieff M, Schirmer U *Klinische Anasthesiologie—Praxisorientierter Leitfaden unter besonderer Berucksichtigung des operativen Vorgehens*. Berlin: Springer-Verlag, 1995

10 Wang LP, Hagerdal M. Reported anaesthetic complications during an 11-year period. A retrospective study. *Acta Anaesthesiol Scand* 1992; **36**: 234–40

11 Tiret L, Desmonts JM, Hatton F, Vourc'h G. Complications associated with anaesthesia—a prospective survey in France. *Can Anaesth Soc J* 1986; **33**: 336–44

12 Andrews B. Reporting of anesthesia-related incidents: the New Jersey experience. *J Clin Monit Comput* 1998; **14**: 71–2

13 Cooper JB, Cullen DJ, Nemeskal R, *et al*. Effects of information feedback and pulse oximetry on the incidence of anesthesia complications. *Anesthesiology* 1987; **67**: 686–94

14 Cohen MM, Duncan PG, Pope WDB, *et al.* The Canadian four-centre study of anaesthetic outcomes: II. Can outcomes be used to assess the quality of anaesthesia care? *Can J Anaesth* 1992; **39**: 430–9

15 Runciman WB, Sellen A, Webb RK, Williamson JA, Currie M, Morgan C. The Australian Incident Monitoring Study. Errors, incidents, and accidents in anaesthesia practice. *Anaesth Intens Care* 1993; **21**: 506–19

16 Cohen MM, Duncan PG, Pope WD, Wolkenstein C. A survey of 112,000 anaesthetics at one teaching hospital (1975–83). *Can Anaesth Soc J* 1986; **33**: 22–31

17 Sanborn KV, Castro J, Kuroda M, Thys DM. Detection of intraoperative incidents by electronic scanning of computerized anesthesia records. *Anesthesiology* 1996; **85**: 977–87

18 Kersting T. Qualitätssicherung und Qualitatskontrolle in der Anasthesie. *Anaesth Intensivmed* 1991; **32**: 308–14

19 Schmidt K, Ladleif P, Hommerich P, Harke H. Qualitätssicherung: Klinikprofile im Vergleich. *Anaesth Intensivmed* 1991; **32**: 315–9

20 Tsekos E, Leier M, Boeden G, Blinzler L, Jagschies I, Heuser D. Qualitatssicherung in der Anästhesie—zwischen Akzeptanz und Realisierung. *Anaesth Intensivmed* 1993; **34**: 325–9

21 Forrest JB, Cahalan MK, Rehder K, *et al.* Multicenter study of general anesthesia. II. Results. *Anesthesiology* 1990; **72**: 262–8

22 Arvidsson S, Ouchterlony J, Nilsson S, Sjostedt L, Svardsudd K. The Gothenburg study of perioperative risk. I. Preoperative findings, postoperative complications. *Acta Anaesthesiol Scand* 1994; **38**: 679–90

23 Pedersen T, Eliasen K, Henriksen E. A prospective study of cardiopulmonary complications associated with anaesthesia and surgery: risk indicators of cardiopulmonary morbidity. *Acta Anaesthesiol Scand* 1990; **34**: 144–55

24 Ouchterlony J, Arvidsson S, Sjostedt L, Svardsudd K Peroperative and immediate postoperative adverse events in patients undergoing elective general and orthopaedic surgery. The Gothenburg study of perioperative risk (PROPER). Part II. *Acta Anaesthesiol Scand* 1995; **39**: 643–52

25 Cooper JB, Newbower RS, Kitz RJ. An analysis of major errors and equipment failures in anesthesia management: considerations for prevention and detection. *Anesthesiology* 1984; **60**: 34–42

26 Bothner U, Georgieff M, Schwilk B. Validation of routine incidence reporting of one anaesthesia provider institution within a nation-wide quality of process assessment program. *J Clin Monit Comput* 1998; **14**: 305–11

27 Jayasuriya JP, Anandaciva S. Compliance with an incidence report scheme in anaesthesia. *Anaesthesia* 1995; **50**: 846–9

28 Lorenzi NM, Riley RT, Blyth AJ, Southon G, Dixon BJ. Antecedents of the people and organizational aspects of medical informatics: review of the literature. *JAMA* 1997; **4**: 79–93

29 Berwick DM. Controlling variation in health care: a consultation from Walter Shewhart. *Med Care* 1991; **29**: 1212–25

30 Schwilk B, Hahnel J, Friess L, Blessing S, Friesdorf W. Ergebnisse zur Verfahrensentwicklung und zum personellen Aufwand im Zusammenhang mit der Einfuhrung qualitatssichernder Massnahmen. *Anasth Intensivmed* 1994; **35**: 349–56

31 Campling EA, Devlin HB, Lunn JN. Reporting to NCEPOD. *BMJ* 1992; **305**: 252

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LABORATORY INVESTIGATION

Effects of protein binding on the placental transfer of propofol in the human dually perfused cotyledon *in vitro*

Y.-L. He*, S. Tsujimoto, M. Tanimoto, R. Okutani, K. Murakawa and C. Tashiro

Department of Anaesthesiology, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya City 663-8501, Japan

**Corresponding author*

The placental transfer of propofol was investigated using the *in vitro* dually perfused cotyledon model of the human placenta, and the effects of protein binding in the foetal perfusate were examined. Both maternal and foetal circulations were perfused in a single-pass mode and >30 min of stabilization was allowed before adding propofol and antipyrine to the maternal perfusate. The placental clearances of propofol were significantly increased by the augmented albumin concentrations in the foetal perfusate (1.68 (SD 0.68), 3.08 (1.55), 4.79 (1.76), 5.75 (1.89) and 7.03 (1.46) ml h^{-1} g^{-1} at the albumin concentrations of 4.4, 11, 22, 33 and 44 g $litre^{-1}$, respectively). Although the total propofol concentration in the foetal vein increased significantly with increasing albumin concentration, the concentration of free propofol remained unchanged. These results indicate that binding to foetal albumin is a determining feature in the control of the placental transfer of propofol, and that the pharmacological effects of propofol on the foetus can be expected to be fairly constant and predictable from the maternal propofol concentration.

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Propofol is becoming increasingly popular in clinical anaesthesia and the sedation of intensive care patients because of its rapid onset, short duration of action, and rapid recovery with a low incidence of postoperative side-effects. Several studies have been performed to evaluate the value and safety of propofol as an induction agent for general anaesthesia in comparison with thiopental in parturients undergoing caesarean section[1–9] and for the maintenance of anaesthesia.[8 9] Opinions on the safety of using propofol in parturients undergoing Caesarean section are divided. Although Celleno and colleagues reported that neonates from mothers who received propofol (2.4–2.8 mg kg^{-1}) had muscular hypotonus, lower Apgar and neurobehavioural scores than those who received thiopental,[3 6] six other centres concluded that propofol (1.5–2.5 mg kg^{-1}) is a suitable alternative to thiopental.[1 2 4 5 7–9] The foetal/maternal ratio of propofol at delivery was reported to be ~0.7,[9–11] demonstrating that propofol diffuses across the placenta efficiently. Lipid solubility, the degree of ionization and the amount of protein binding are considered to influence the placental permeability of a drug. Propofol is a highly lipophilic compound and is extensively bound to plasma proteins (97–99%),[12–14] and drugs of this type are generally believed to bind to albumin in plasma. Therefore, the changes in concentrations of proteins such as albumin may have considerable effects on placental permeability and unbound drug, which is the pharmacologically active form. There are many practical difficulties in studying the factors governing the placental transfer of drugs in parturients. The *in vitro* perfused human placental preparation has been shown to be a useful model[15–21] for the accurate examination of the determinant(s) of the placental transfer of a drug, as it allows perfusate components to be manipulated without concern for the mother or foetus. The object of the present study was to investigate the placental transfer of propofol and the effects of protein binding in the foetal perfusate using the dually perfused human placental model.

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Materials and methods

Placental perfusion

This study was approved by our institutional review board. Placentas from healthy parturients were obtained after Caesarean section and transported immediately to the laboratory. Foetal and maternal sides of the placenta were perfused following the method used in the *in vitro* perfusion model reported previously.[22] An intact placental lobule was selected by inspecting the maternal side, and a chorionic artery and vein supplying a single peripheral cotyledon were cannulated. Figure 1 shows a schematic diagram of the perfusion system. The foetal circuit was perfused at the rate of 2.0 ml min^{-1}. The cotyledon was then mounted in a specially designed chamber maintained at 37°C in a water bath, with the foetal surface of the placenta facing downwards. Three 20 G needles were gently placed in the decidual plate and the intervillous space was perfused at 15 ml min^{-1}. Both foetal and maternal circuits were perfused in single-pass mode with tissue culture medium 199 modified with Earl's salts (ICN Biomedicals, Aurora, OH, USA) containing heparin 2500 u litre^{-1}, gentamicin 50 mg litre^{-1} and glucose 1.0 g litre^{-1}. Human serum albumin (HSA) (plasma protein fraction; Baxter, Tokyo, Japan) was added to obtain desired HSA concentrations, and dextran (mol.wt 40 000; Wako Pure Chemicals, Osaka, Japan) was added to adjust the oncotic pressure. Sodium bicarbonate was added to keep the pH of the perfusate within the physiological range. Foetal and maternal perfusion pressures were measured with a sphygmomanometer (Yamasu, Tokyo, Japan). After a stabilization period of >30 min, propofol (Diprivan; Zeneca Pharmaceuticals, Osaka, Japan) and antipyrine (Wako Pure Chemicals, Osaka, Japan) were added to the maternal perfusate. The placental experiment was initiated at the albumin concentration of 4.4 g litre^{-1} in both circuits and returned to the same condition at the end of the perfusion experiment. In the intervening period, the albumin concentrations in foetal perfusate were varied at random among 11, 22, 33 and 44 g litre^{-1} at 30-min intervals, while the albumin concentration in the maternal perfusate was maintained at 4.4 g litre^{-1}. Eight placentas were successfully perfused and three or four clearance estimations with different albumin concentrations in the foetal perfusate were performed in each placental preparation depending on tissue viability. Arterial and venous samples from the maternal circuit and venous samples from the foetal circuit were taken at 20 and 30 min during each experimental period for propofol and antipyrine measurement. A pilot single-pass perfusion experiment with foetal venous samples taken at 2, 5, 10, 15, 20 and 30 min demonstrated that propofol and antipyrine concentrations reached a plateau by 10 min. To measure the protein binding of propofol at different albumin concentrations, venous samples from the foetal circuit were collected during periods of 20–30 min. Venous samples were also taken from the foetal and maternal circuits at 30-min intervals for the measurement of human chorionic gonadotropin (hCG) concentration. The synthesis and release of hCG by the syncytiotrophoblast is a direct indication of the metabolic activity of the perfused cotyledon. Additional arterial and venous samples were taken for the measurement of glucose and lactate concentrations, to estimate glucose consumption and lactate production. At the end of the experiment, perfused placental tissue was dissected and weighed, and the concentrations of propofol and antipyrine were determined.

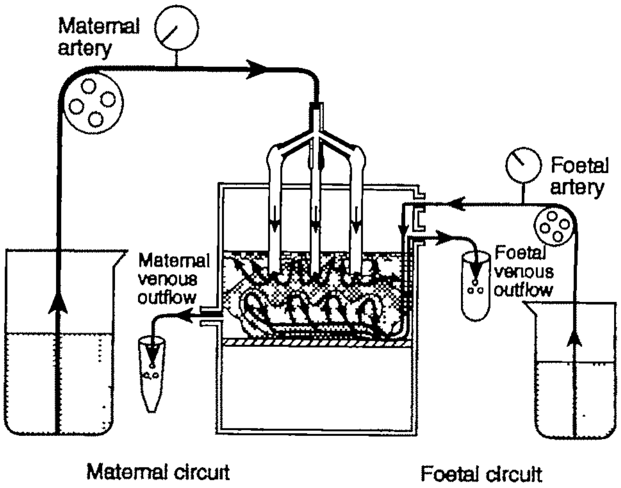

Fig 1 Schematic representation of the experimental setup for perfusing a human placental cotyledon *in vitro*.

Sample analysis

Propofol and antipyrine were measured using modified high-performance liquid chromatography (HPLC) methods reported previously by Plummer[23] and Ha *et al.*,[24] respectively. The HPLC apparatus (LC-10AD; Shimadzu, Kyoto, Japan) comprised a variable-wavelength UV detector (SPD-10AD; Shimadzu) and fluorimetric detector (RF-10AD; Shimadzu), a degasser (DGU-14A; Shimadzu), an auto-injector (SIL-10AD; Shimadzu) and a column oven (CTO-10AS; Shimadzu). Briefly, a Symmetry C18 column (3.5 µm, 4.6×100 mm; Waters, Japan) was used for propofol analysis with fluorometric detection. For antipyrine, a Nova-PakR C18 column (4.0 µm, 3.9×150 mm; Waters) was used with the UV detector set at 210 nm. Placental tissue homogenate (10%) was prepared with the mobile phase for propofol measurement. Both perfusate and tissue homogenate samples were deproteinized with 10 volumes of acetonitrile, and 10 µl of the supernatant was injected onto the chromatograph. The intra- and inter-assay variabilities for propofol and antipyrine were <5% over the concentration range studied. The perfusate concentrations of hCG were measured by enzyme immunoassay using an IMx^{TM} hCG Dinapack (Dainabot, Tokyo, Japan). Glucose and lactate concentrations were measured using a blood gas, electrolyte, metabolite analyser (ABL system 625; Radiometer, Copenhagen, Denmark).

Measurement of propofol binding

The unbound fraction of propofol in the perfusate samples was determined by an ultrafiltration method using the Centrifree™ Micropartition System (Amicon, Bedford, MA, USA).

Calculations of clearance and clearance index

The placental transfer of propofol and antipyrine was evaluated as transplacental clearance. A single-pass experimental design was used for both maternal and foetal circulations. The transplacental clearance was then calculated as follows:[22]

$$CL = \frac{C_{fv} \cdot Q_f}{C_{ma}} \qquad (1)$$

where Q_f is the flow rate of the foetal circulation, C_{fv} and C_{ma} are the venous concentration in the foetal circuit and the arterial concentration in the maternal circuit, respectively. Transplacental clearance was estimated at 20 and 30 min in each perfusion period at different albumin concentrations in the foetal perfusate. The clearance index (CI) of propofol was calculated based on the transplacental clearances of propofol ($CL_{propofol}$) and antipyrine ($CL_{antipyrine}$), as follows:

$$CI = \frac{CL_{propofol}}{CL_{antipyrine}} \qquad (2)$$

Statistics

All data are expressed as mean (SD). SigmaStat for Windows (Version 1.0; Jandel Scientific, Chicago, IL, USA) was used for the statistical analysis. The propofol concentrations, transplacental clearances and clearance indexes were analysed by one-way repeated measures analysis of variance. If the analysis of variance was found to be significant, Bonferroni's test was performed to compare the values at various albumin concentrations in the foetal perfusate with that at 4.4 g litre^{-1}. The significance of the difference between placental tissue and maternal venous concentrations of propofol was evaluated with the paired t-test. Differences were considered to be significant when $P<0.05$.

Results

The characteristics of the perfused cotyledons are summarized in Table 1. Glucose consumption, lactate production and the production of hCG showed values similar to those reported previously,[25–26] indicating the physiological integrity of the perfused cotyledons. No hCG was detected in the foetal circulation, suggesting the expected preferential secretion of the hormone and the physical integrity of the placental preparation.

Table 1 Characteristics of the perfused human placentas. All data are expressed as mean (SD)

Placenta weight	538 (77) g
Cotyledon weight	16.5 (5.5) g
Maternal pressure	21 (7) mm Hg
Foetal pressure	70 (19) mm Hg
Glucose consumption	0.296 (0.044) mmol min^{-1} g^{-1}
Lactate production	0.362 (0.094) mmol min^{-1} g^{-1}
hCG	5.514 (2.810) i.u. h^{-1} g^{-1}

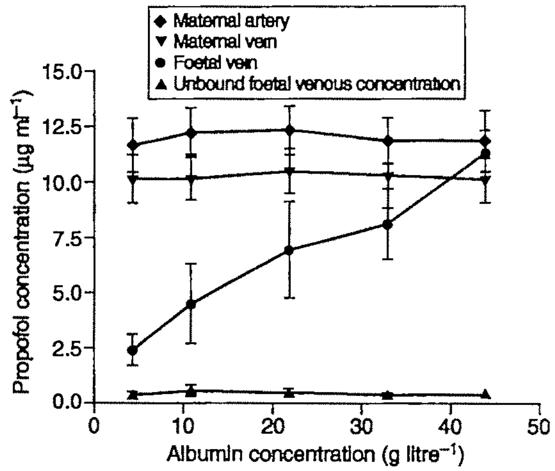

Fig 2 Propofol concentrations in maternal artery (diamond), maternal vein (down filled triangle), foetal vein (filled circle), and the unbound foetal venous concentrations (up filled triangle) at various concentrations of human serum albumin in the foetal perfusate.

Propofol was detected in foetal samples within 2 min, suggesting that propofol passes across the placenta rapidly. The propofol concentrations in the maternal artery, vein and foetal vein at various albumin concentrations in the foetal perfusate are illustrated in Figure 2. The foetal venous propofol concentrations increased significantly as the albumin concentration increased from 4.4 to 11, 22, 33 and 44 g litre^{-1} ($P<0.05$), while the maternal venous propofol concentration remained unchanged. The propofol concentration in the foetal vein increased to the level found in maternal circulation when the albumin concentration in the foetal perfusate was maintained at the physiological level of 44 g litre^{-1}, resulting in a foetal/maternal concentration ratio of 1.13 (SD 0.15). In contrast, the concentration of free propofol in the foetal vein was not significantly affected by the albumin concentration (Fig. 2).

Figure 3 illustrates the effects of albumin concentration in the foetal circulation on the transplacental clearances of propofol and antipyrine and the clearance indexes. The placental clearance of antipyrine, which is commonly used as a reference compound in placental perfusion, did not change significantly at a variety of albumin concentrations over the range of 3.23 (SD 1.1) to 3.90 (1.40) ml h^{-1} g^{-1} (Fig. 3). The placental clearance of propofol was 1.68 (0.68)

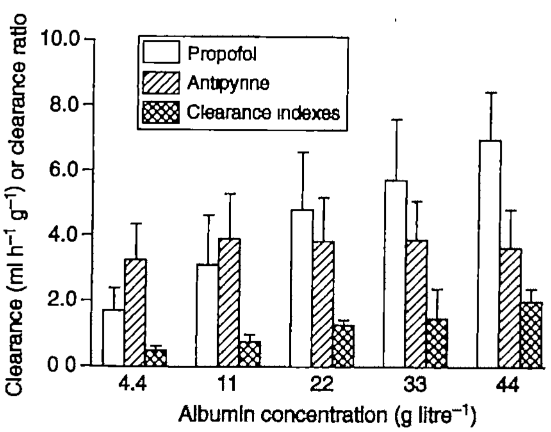

Fig 3 Effects of human serum albumin concentrations in the foetal perfusate on the transplacental clearances of propofol (open columns), antipyrine (hatched columns) and clearance indexes (cross-hatched columns).

ml h^{-1} g^{-1} at the albumin concentration of 4.4 g $litre^{-1}$, with a clearance index of 0.51 (0.09). It was significantly increased to 3.08 (1.55), 4.79 (1.76), 5.75 (1.89) and 7.03 (1.46) ml h^{-1} g^{-1} by increasing the albumin concentrations to 11, 22, 33 and 44 g $litre^{-1}$, respectively ($P<0.05$). Consequently, the clearance index exceeded unity when the albumin concentration was ≥22 g $litre^{-1}$ (0.76 (0.20), 1.29 (0.19), 1.49 (0.21) and 2.01 (0.40) at albumin concentrations of 11, 22, 33 and 44 g $litre^{-1}$, respectively). The mean propofol concentration in the perfused placental tissue at the end of the experiments was 53.3 (20) µg g^{-1} wet tissue, which was significantly higher than the corresponding mean maternal venous concentration (9.7 (0.9) µg ml^{-1}; $P<0.001$).

Discussion

In obstetric anaesthesia, the concern has generally been to minimize foetal exposure, but the foetus has now also become the object of intended drug treatment,[27] which is usually administered via the maternal circulation. Knowledge about the placental transfer and uptake of anaesthetics and the factors that may influence transplacental passage should gain increasing therapeutic importance in obstetric anaesthesia for foetal therapy. The commonly used foetal/maternal concentration ratio varies, depending on factors such as the interval between drug administration and delivery, and the protein binding of a drug in maternal and foetal plasma.[28] Thiopental, which is the most commonly used induction agent in obstetrics, crosses the placenta rapidly and can be detected in umbilical blood within 30 s of its administration to the mother.[29] The mean foetal/maternal ratio for thiopental has been reported to be in the range of 0.4–1.0.[30] Albumin concentrations in both mother and foetus are reported to show dynamic changes during pregnancy.[31] The maternal and foetal albumin concentrations were shown to range between 25 and 35 g $litre^{-1}$ and between 7.5 and 39.8 g $litre^{-1}$, respectively, over weeks 12–40 of gestation.[31] In this study, the placental transfer of propofol was investigated using the perfused human placental model, which allowed us to simulate this *in vivo* situation by varying the albumin concentration in the foetal circulation from 4.4 to 44 g $litre^{-1}$.

Antipyrine serves as an ideal marker of placental transfer because it is of intermediate solubility and does not bind to plasma proteins. The placental clearance of antipyrine remained unchanged throughout the experimental period at different albumin concentrations in the foetal perfusate (Fig. 3), suggesting that the transplacental exchange of small molecules was maintained throughout the perfusion period. The transplacental clearance of propofol increased considerably with increasing albumin concentration, and was significantly greater than that of antipyrine when the albumin concentration in the foetal circulation was ≥22 g $litre^{-1}$. This result indicates that the placental permeability of propofol might be more efficient than that for antipyrine during the pregnancy period close to term. Increasing the albumin concentration in the foetal perfusate led to a significant increase in the placental transfer rate of propofol, demonstrating that binding to albumin in the foetal circulation is a dominant feature in the control of the placental transfer of propofol. Binding of propofol to plasma was reported to be independent of the substrate concentration over the range 0.04–150 mg ml^{-1};[32] therefore, the binding capacity for propofol is expected to be proportional to the albumin concentration according to the formula $B/F = nK_aP$, where B is the bound drug concentration, F is the unbound drug concentration, n is the number of binding sites per molecule of protein, K_a is the affinity constant and P is the concentration of binding protein.[33] Consistent with this suggestion, the observed unbound fractions of propofol in foetal venous samples were 16.9 (SD 3.6), 12.7 (3.3), 6.8 (1.5), 4.2 (1.1) and 2.8 (0.5)% at albumin concentrations of 4.4, 11, 22, 33 and 44 g $litre^{-1}$, respectively. Therefore, the facilitated placental transfer of propofol can be readily explained by the differences in protein-binding capacity at various albumin concentrations, because the increased protein-binding capacity for propofol at higher albumin concentrations in the foetal perfusate allows a larger amount of the drug to cross the placenta faster. This is consistent with observations using the same perfused human placenta model with several other lipophilic drugs, including thiopental, demonstrating that transplacental distribution was markedly influenced by maternal and foetal protein capacity.[17 20 34–37]

The placenta is unique in being perfused on both its maternal and its foetal surface, and foetal blood is separated from that of the mother by the placental trophoblast and the foetal capillary system. Therefore, the transplacental exchange of a drug comprises three processes: distribution from the maternal circulation to the placenta; placental sequestration, including intracellular binding to placental component(s) and placental metabolism; and transfer out of the placenta to the foetal and maternal circulations. The maternal venous concentrations were not influenced by the albumin concentration in the foetal perfusate, resulting in constant extraction of propofol from the maternal circulation, which was about 15% (Fig. 2). Therefore the considerable facilitation of the transplacental exchange of propofol by increased albumin concentrations can be attributed to the facilitated placental sequestration of propofol from the placenta to the foetal circulation. That is, the placental transfer of propofol is restricted by placental retention at lower albumin concentrations in the foetal perfusate. Consistent with this, high placental tissue concentrations of propofol (53.3 (20) μg ml^{-1}) were observed at the end of the experiment. This implies that the placenta plays an important role in protecting the foetus from exposure to propofol administered to the mother as a depot. On the basis of a simple model that has been proposed to interpret the effects of binding to serum albumin and to the placenta on the placental transfer of a drug,[35] the protein-binding capacity and the relative affinity of propofol for maternal and foetal plasma proteins and to placental component(s) can be considered to be the predominant features of the control of transfer across the placenta. Furthermore, restricted foetal transfer associated with pronounced placental accumulation for lipophilic drugs, such as bupivacaine, dexmedetomidine and sufentanil, has also been reported.[17 18 20 21]

The foetal/maternal concentration ratio of propofol varied with the albumin concentration in the foetal perfusate, ranging from 0.74 (0.28) to 1.13 (0.15) over the albumin concentration range of 22–44 g $litre^{-1}$ in this human perfused cotyledon model. This indicates that the clinically measured foetal/maternal ratio, which is considered to be an index of the placental transfer of a drug, can show a wide range depending on the plasma protein concentrations. It is of note that the free concentrations of propofol in the foetal perfusate did not change significantly, irrespective of the considerably increased total propofol concentrations (Fig. 2). Therefore, the pharmacological effects of propofol will not be influenced by the plasma albumin concentration in the foetus. However, *in vivo*, foetal uptake of propofol is a dynamic process, and on the basis of the lower umbilical arterial concentrations compared with those in umbilical vein samples it has been suggested that the neonate continues to take up propofol during delivery, a process that may involve neonatal metabolism.[9] Protein binding can be seen as a mechanism whereby propofol is transported to and from the peripheral tissues; therefore, the storage function of plasma protein binding should not be neglected. The enormously increased bound component in the foetus at higher albumin concentrations might result in a prolonged effect of propofol on the foetus, and more importantly, on the neonate after birth.

In summary, placental transfer of propofol was significantly facilitated by increased albumin concentrations in the foetal circulation, indicating that the binding capacity to albumin in the foetal circulation is a dominant feature in the control of the transplacental exchange. The high propofol concentration in placental tissue demonstrates that the placenta plays an important role in protecting the foetus from exposure to propofol administered to the mother as a depot. The free concentration of propofol did not change significantly despite the considerably increase in total propofol concentration in the foetal circulation associated with the increased albumin concentration, suggesting that the pharmacological effect of propofol on the foetus can be expected to be fairly constant and predictable from the maternal propofol concentration. However, the storage function of plasma protein binding should not be neglected.

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References

1 Moore J, Bill KM, Flynn RJ, McKeating KT, Howard PJ. A comparison between propofol and thiopentone as induction agents in obstetric anaesthesia *Anaesthesia* 1989, **44**: 753–7

2 Valtonen M, Kanto J, Rosenberg P. Comparison of propofol and thiopentone for induction of anaesthesia for elective caesarean section. *Anaesthesia* 1989, **44**: 758–62

3 Celleno D, Capogna G, Tomassetti M, Costantino P, Di Feo G, Nishi R. Neurobehavioral effects of propofol on the neonate following elective caesarean section. *Br J Anaesth* 1989; **62**: 649–54

4 Gin T, Gregory MA, Oh TE. The hemodynamic effects of propofol and thiopentone for induction of caesarean section. *Anaesth Intens Care* 1990, **18**: 175–9

5 Siafaka I, Vadalouca A, Gatziou B, Petropoulos G, Salamalekis E. A comparative study of propofol and thiopental as induction agents for elective caesarean section *Clin Exp Obstet Gynecol* 1992; **19**: 93–6

6 Celleno D, Capogna G, Emanuelli M, Varrassi G, Muratori F, Costantino P, *et al.* Which induction drug for caesarean section? A comparison of thiopental sodium, propofol, and midazolam. *J Clin Anesth* 1993; **5**: 284–8

7 Gin T, O'Meara ME, Kan AF, Leung RK, Tan P, Yau G. Plasma catecholamines and neonatal condition after induction of anaesthesia with propofol or thiopentone at caesarean section. *Br J Anaesth* 1993; **70**: 311–6

8 Abboud TK, Zhu J, Richardson M, Peres Da Silva E, Donovan M. Intravenous propofol vs thiamylal–isoflurane for caesarean section: comparative maternal and neonatal effects. *Acta Anaesthesiol Scand* 1995; **39**: 205–9

9 Dailland P, Cockshott ID, Lirzin JD, Jacquinot P, Jorrot JC, Devery J, *et al.* Intravenous propofol during caesarean section. placental transfer, concentrations in breast milk, and neonatal effects. A preliminary study *Anesthesiology* 1989, **71**: 827–4

10 Gin T, Gregory MA, Chan K, Oh TE. Maternal and fetal levels of propofol at Caesarean section. *Anaesth Intens Care* 1990; **18**: 180–4

11 Gin T, Yau G, Jong W, Tan P, Leung RKW, Chan K. Disposition of propofol at caesarean section and in the postpartum period *Br J Anaesth* 1991; **67**. 49–53

12 Servin F, Desmonts JM, Haberer JP, Cockshott ID, Plummer GF, Farinotti R. Pharmacokinetics and protein binding of propofol in patients with cirrhosis. *Anesthesiology* 1988; **69**: 887–91

13 Kirkpatrick T, Cockshott ID, Douglas EJ, Nimmo WS. Pharmacokinetics of propofol (Diprivan) in elderly patients. *Br J Anaesth* 1988; **60**: 146–50

14 Cockshott ID, Douglas EJ, Plummer GF, Simons PJ. The pharmacokinetics of propofol in laboratory animals. *Xenobiotica* 1992; **22**: 369–75

15 Schneider H and Dancis J, eds. In vitro perfusion of human placental tissue. *Contributions to Gynecology and Obstetrics*, Vol. 13. Basel: Karger, 1985: 1–189

16 Zakowski M, Ham AA, Grant GJ. Transfer and uptake of alfentanil in the human placenta during in vitro perfusion. *Anesth Analg* 1994; **79**: 1089–93

17 Johnson RF, Herman N, Arney TL, Gonzalez H, Johnson HV, Downing JW. Bupivacaine transfer across the human term placenta. *Anesthesiology* 1995; **82**: 459–68

18 Ala-Kokko TI, Pienimaki P, Herva R, Hollmen AI, Pelkonen O, Vanakangas K. Transfer of lidocaine and bupivacaine across the isolated perfused human placenta. *Pharmacol Toxicol* 1995; **77**: 142–8

19 Johnson RF, Herman N, Johnson HV, Arney TL, Paschall RL, Downing JW. Effects of fetal pH on local anesthetic transfer across the human placenta. *Anesthesiology* 1996; **85**: 608–15

20 Johnson RF, Herman N, Arney TL, Johnson HV, Paschall RL, Downing JW. The placental transfer of sufentanil: effects of fetal pH, protein binding, and sufentanil concentration. *Anesth Analg* 1997; **84**: 1262–8

21 Ala-Kokko TI, Pienimaki P, Lampela E, Hollmen AI, Pelkonen O, Vanakangas K. Transfer of clonidine and dexmedetomidine across the isolated perfused human placenta. *Acta Anaesthesiol Scand* 1997; **41**: 313–9

22 Schneider H, Panigel M, Dancis J. Transfer across the perfused human placenta of antipyrine, sodium, and leucine. *Am J Obstet Gynecol* 1972; **114**: 822–8

23 Plummer GF. Improved method for determination of propofol in blood by high-performance liquid chromatography with fluorescence detection. *J Chromatog* 1987; **421**: 171–6

24 Ha H, Funk B, Gerber HR, Follath F. Determination of bupivacaine in plasma by high-performance liquid chromatography. *Anesth Analg* 1984; **63**: 448–50

25 Miller RK, Wier PJ, Maulik D, di Sant'Agnese PA. Human placenta in vitro: characterization during 12 h of dual perfusion. *Contrib Gynec Obstet* 1985, **13**: 77–84

26 Connell GR, Klucj RM, Hamilton SE, Mortimer RH, Hooper WD, Dickinson RG. Markers of physical integrity and metabolic viability of the perfused human placental lobule. *Clin Exp Pharmacol Physiol* 1988; **15**: 837–44

27 Ward RM. Pharmacological treatment of the fetus. Clinical pharmacokinetic considerations. *Clin Pharmacokinet* 1995; **28**: 343–50

28 Morgan DJ. Drug disposition in mother and foetus. *Clin Exp Pharmacol Physiol* 1997; **24**: 869–73

29 Kosaka Y, Takahashi T, Mark LC. Intravenous thiobarbiturate anesthesia for Cesarean section. *Anesthesiology* 1969; **31**: 489–506

30 Reynolds F. Placental transfer of drugs used by anaesthetics. In: Kaufman L, ed. *Anaesthesia Reviews*, Vol. 6. Churchill Livingstone, Edinburgh, 1989: 163–4

31 Krauer B, Dayer P, Anner R. Changes in serum albumin and $\alpha 1$-acid glycoprotein concentrations during pregnancy: an analysis of fetal-maternal pairs. *Br J Obstet Gynaecol* 1984; **91**: 875–81

32 Altmayer P, Buch U, Buch HP. Propofol binding to human blood proteins. *Arzneim Forsch Drug Res* 1995; **45**: 1053–6

33 Martin DH, Abramson FP. The significance of plasma protein binding on fetal/maternal distribution of drugs at steady-state. *Clin Pharmacokinet* 1988; **14**: 156–70

34 Herman NL, Li AT, Bjoraker R, Johnson RF, Van Decar TK, Downing JW, *et al.* The effects of maternal–fetal perfusate protein differences on the bidirectional transfer of thiopental across the human placenta *Anesthesiology* 1998; **89**: A1046

35 Dancis J, Jansen V, Levitz M. Placental transfer of steroids: effect of binding to serum albumin and to placenta. *Am J Physiol* 1980; **238**: E208–13

36 Hamshaw-Thomas A, Rogerson N, Reynolds F. Transfer of bupivacaine, lidocaine and pethidine across the rabbit placenta: influence of maternal protein binding and fetal flow. *Placenta* 1984; **5**: 61–70

37 Schmolling J, Jung S, Reinsberg J, Schlebush H. Digoxin transfer across the isolated placenta is influenced by maternal and fetal albumin concentrations. *Reprod Fertil Dev* 1996; **8**: 969–74

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REVIEW ARTICLE

Serum S100 protein as a marker of cerebral damage during cardiac surgery

M. Shaaban Ali, M. Harmer and R. Vaughan

Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Heath Park, Cardiff CF14 4XN, UK

The identification of a serum marker to assist in the diagnosis of cerebral injury after cardiac surgery is potentially useful. S100 protein is an early marker of cerebral damage. It is released after cardiac surgery performed under cardiopulmonary bypass (CPB). Its level is correlated with the duration of CPB, deep circulatory arrest and aortic cross-clamping. Increased levels of S100 protein are correlated with the age of the patient and the number of microemboli, especially during aortic cannulation. Perioperative cerebral complications such as stroke, delayed awakening and confusion are associated with increased levels of S100 protein directly after bypass and from 15 to 48 h after it. In addition, increased levels of S100 protein are related to neuropsychological dysfunction after cardiac surgery. S100 protein has early and late release patterns after CPB; the early pattern may be due to sub-clinical brain injury. The late release pattern may be due to perioperative cerebral complications. Patients undergoing intra-cardiac operations combined with coronary artery bypass surgery are more susceptible to brain injury and have higher levels of S100 after CPB. Furthermore, adults and children undergoing deep circulatory arrest are more susceptible to brain injury, in terms of higher S100 protein release after CPB. Serum S100 protein levels are reduced after using arterial line filtration and covalent-bonded heparin to coat the inner surface of the CPB circuit.

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Despite advances in anaesthesia, cardiopulmonary bypass (CPB) and surgical techniques, cerebral injury remains a major source of morbidity after cardiac surgery.[9 25 51 58 69 71 78] The diagnosis of cerebral injury currently relies on clinical neurological examination, computed axial tomography (CT) or magnetic resonance imaging (MRI). However, these methods are not always suitable for use immediately after cardiac surgery when patients may be unconscious, sedated and artificially ventilated, or haemodynamically unstable, and thus unable to cooperate. The identification of a biochemical serum marker to assist in the diagnosis of cerebral injury would potentially be useful.

One way to demonstrate the adequacy of a particular biochemical marker is to establish a correlation between a plasma level and neurological or neuropsychological outcome. Another possibility would be to establish an association with some variable that is considered relevant to the neuropsychological outcome, for example number of microemboli,[68 69] duration of CPB,[47] or the use of arterial filters.[68] Other methods might involve changing the CPB strategy or surgical technique, or using neuroprotective drugs (e.g. GM_1 ganglioside,[30] magnesium sulphate ($MgSO_4$)[40 53 56 57 84]) or anti-inflammatory drugs (e.g. methylprednisolone, aprotinin[29]), to study the effect of this change or 'beneficial effect' on biochemical marker levels.[42]

S100 protein is an early marker for brain damage, which might be valuable to gauge the timing and extent of cerebral damage after CPB. Recently, elevated serum levels of S100 have been detected after adult cardiac operations complicated by neurological injury.[5 10 93]

In this review, the pattern of S100 protein release and its relation to postoperative neurological outcome after cardiac operations with different CPB techniques will be discussed.

What is S100 protein?

In 1965, Moore isolated a subcellular fraction from bovine brain, which was thought to contain nervous system-specific

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proteins.[62] This fraction was called S100 because the constituents were soluble in 100% saturated ammonium sulphate at neutral pH. The S100 protein family contains ~16 members based on amino acid sequence homology and similar structural properties.[95] S100 protein is an acidic calcium-binding protein (molecular weight 21 kDa) found in high concentrations in glial and Schwann cells. It exists in various forms depending on alpha or beta unit configuration. The beta subunit is highly brain specific. The beta-beta (S100β) units are present in glial and Schwann cells, the alpha-beta (S100 αβ) subunits appear in glial but not in Schwann cells,[6,39] whereas alpha-alpha (S100a0) subunits are present in striated muscles, heart and kidney. S100 protein is metabolized in the kidney and excreted in urine, and has a biological half-life of ~2 h.[91]

The exact functions of S100 proteins are not well known. As S100 proteins are mostly present intracellularly, the majority of the molecules will function as intracellular calcium receptor proteins.[95] In addition, Zimmer and colleagues suggested that S100 proteins modulate a wide range of intracellular processes including inter-cell communication, cell structure, growth, energy metabolism, contraction and intracellular signal transduction. Furthermore, S100β protein is involved in promoting axonal growth, glial proliferation, neuronal differentiation and calcium homeostasis.[18,34,77] More importantly, S100β protein is considered as a contributing factor in Alzheimer's disease and acquired immune deficiency syndrome (AIDS).[54,82] Interestingly, studies using animal models have suggested that extracellular S100 protein may play a role in learning and memory.[20,45]

S100 protein assay

Two methods for S100 protein analysis have been described.

(1) Monoclonal two-site immunoradiometric assay (Sangtec 100; Sangtec Medical AB, Bromma, Sweden), which has a lower detection limit of 0.2 μg litre^{-1}.[93]

(2) Immunoluminometric assay (Sangtec LIA100; AB Sangtec Medical, Bromma, Sweden) which can measure S100 protein to 0.02 μg litre^{-1}.[3]

Both types of assay use three monoclonal antibodies (SMST12, SMSK 25, SMSK 28) to detect the β chains in the ββ and αβ dimers of S100 protein.

S100 protein is normally not detectable in serum, but appears after a stroke, subarachnoid haemorrhage, head injury or CPB.[35,42,66,67,93] The lower limit of detection ranges from 0.02 to 0.2 μg litre^{-1}, depending on the type of assay.[3,93] S100 protein levels in excess of 0.5 μg litre^{-1} are considered pathological.[93]

S100 protein is thermostable and its assay is not affected by heparin, protamine or propofol.[21] Similarly, haemolysis has no effect on the analysis of S100 protein samples.[22] Samples can therefore be taken throughout surgery involving CPB. S100 protein is stable on storage of the whole blood sample for up to 48 h, either room temperature or at 4°C, before and after CPB operations.[75]

S100 protein release in non-cardiac surgery patients

S100 protein in pathological conditions

Increased levels of S100 protein have been observed in Alzheimer's disease, dementia associated with Down's syndrome and in AIDS. Elevation of serum S100 protein is directly related to an increased gene expression.[2,31,82] In fact, the position of the S100β gene is on the long arm of chromosome 21 which is also involved in the translocation causing Down's syndrome.[17]

Interestingly, Lindberg and colleagues[49] found high levels of S100 protein before and after CPB in children with Down's syndrome. However, there was no significant change in S100 protein concentrations after CPB compared with the pre-bypass levels. The authors[49] suggested that the increased concentrations of S100 protein in children with Down's syndrome may be explained by duplication of chromosome 21, possibly in conjunction with a more permeable blood–brain barrier.

In Alzheimer's disease, there is DNA amplification in regions near to the localization site of S100β protein. However, the correlation between the increased levels of S100 protein and features seen in Alzheimer's disease or Down's syndrome is not clear.[55] It is possible that the abnormally high S100 protein levels could induce alterations in neurite outgrowth, and glial cell proliferation and morphology, and also affect calcium homeostasis leading to cell death.[17]

S100 protein after minor head injury

Ingebrigsten and colleagues[38] reported increased serum levels of S100 protein after minor head injury. Minor head injury is characterized by a lack of demonstrable focal neurological deficit and apparent clinical recovery.[92] But, Waterloo and colleagues[92] found that the raised levels of S100 protein after minor head injury are associated with specific dysfunction on tests of attention, 12 months after injury. The authors suggested that the increased serum levels of S100 protein may be of prognostic value for long-standing neurocognitive abnormalities after minor head injury.[92]

S100 protein in patients with acute stroke

High S100 protein concentrations have been detected in 71–81% of patients with acute ischaemic stroke, but not in healthy subjects.[15,19] Patients with detectable S100 protein had significantly larger brain lesions. S100 protein levels were increased in patients with larger infarctions at 10 h and thereafter following the onset of symptoms.[19] Neurological

Table 1 Changes in S100 protein levels (median) in four groups of patients undergoing cardiothoracic surgical procedures with or without CPB (Kumar and colleagues)[48]

	Group 1–lung resection	Group 2–CABG	Group 3–aortic root replacement	Group 4–aortic root replacement with circulatory arrest
Mean age, years	66	58	56	64
Number of patients	4	6	4	5
Mean duration of CPB, min	—	100	111	109
Temperature, °C	37	32	28	18
Serum level of S100 after CPB, μg litre^{-1} (median)	—	0.5	1.3	2.3

outcome scores, as assessed by the Scandinavian stroke scale,[76] were inversely correlated with serum levels of S100 protein determined after 10 h (r=–0.56, $P<0.05$), 24 h (r=–0.8, $P<0.05$) and 72 h (r=–0.78, $P<0.05$). Three patients who had fatal outcomes had the highest serum S100 concentrations.[19]

The peak levels of S100 protein were recorded on the third day after the stroke.[15, 61] Missler and colleagues[61] found that the peak levels were correlated with the infarct volume when measured by volumetric CT scan (r=0.75, $P<0.001$), and with the clinical outcome assessed by the Glasgow outcome scale (r=0.51, $P<0.001$). In addition, Büttener and colleagues[15] observed that patients with severe neurological deficits on admission, extensive infarction and the space-occupying effect of ischaemic oedema, had significantly higher serum S100 protein concentrations. These studies suggest that serum S100 protein concentration during acute stroke is a useful marker of infarct size and clinical outcome. Furthermore, it might be useful in monitoring the effects of new therapies in acute cerebral disease.

S100 protein after cardiac arrest

Rosén and colleagues[72] used S100 protein levels for prognostic evaluation in 41 patients after cardiac arrest. The highest levels of S100 protein were found on the first day after arrest. Moreover, S100 protein levels on day 2 correlated with the degree of coma (r=0.49, $P<0.01$) and the period of anoxia on days 1 and 2 (r=0.50, $P<0.01$, and r=0.60, $P<0.01$, respectively). Interestingly, all patients with a S100 protein level ≥0.2 μg litre^{-1} on day 2 after cardiac arrest died within 14 days, and 89% of patients with levels below this value survived. It is clear that the increase in S100 protein after cardiac arrest reflects the degree of hypoxic brain damage and can help to predict the short-term outcome.

Cardiac surgery and S100 protein

Patterns of S100 protein release after cardiac surgery

Adult cardiac surgery

Blomquist and co-workers[10] studied the pattern of S100 protein release during and after cardiac surgery. In one group of patients, samples were collected after heparin administration, 20 min after the start of CPB, at the end of CPB, and then at 3, 6, 12, 24 and 48 h after the end of CPB. In a second group, the course of S100 protein release was defined by samples taken before anaesthesia; before the start of surgery; before the administration of heparin; and at 10 and 40 min after the start of CPB. At the end of CPB, samples were collected every 15 min for 90 min; thereafter samples were taken at 2, 3, 4, 5, 6, 8, 10 and 20 h after CPB. In the first group, detectable concentrations of S100 protein were found 20 min after the start of CPB. Maximum levels (mean (SD), 2.43 (0.3) μg litre^{-1}) occurred at the end of CPB; thereafter concentrations declined to 1.2 (0.2) μg litre^{-1} at 3 h after the end of CPB. An increase in S100 protein level was observed at 5 h post-CPB and was followed by a steady decrease throughout the period of study. In the second group, a similar pattern was observed. Maximum levels of S100 protein (1.96 (0.38) μg litre^{-1}) were noted at the end of CPB. The levels then stabilized 5 h after CPB, followed by a steady decrease until the end of the study. Before CPB, anaesthesia of 2 h or more in combination with surgery did not initiate any release of S100 protein into serum. Westaby and colleagues[93] confirmed that elevations in serum levels of S100 did not occur in patients who underwent coronary artery bypass surgery without CPB. Furthermore, S100 did not appear in the serum of patients who had thoracic surgery without CPB[48] (Table 1).

However, CPB is associated with the release of brain-specific S100 protein, thus indicating an injury to the blood–brain barrier or neuronal cell injury.[32, 42, 93] The highest level of S100 protein occurred at the end of CPB and was followed by a continuous decline.[10, 93] The delay in elimination of S100 protein observed 5 h[10] after the peak levels might indicate a secondary release of S100 protein due to injury caused by re-establishment of pulsatile perfusion.[79] Recently, Gao and colleagues[24] found the peak levels of S100 protein at the end of rewarming (mean (SEM), 1.65 (0.23) μg litre^{-1}) decreased significantly by the end of the operation, and returned to pre-bypass concentrations by the second day after surgery. Furthermore, the peak level of S100 protein occurred at the end of warm CPB (temperature 37°C), with a slight, but not significant, increase at the end of cold CPB (temperature 32°C).[23] Unlike Gao and colleagues,[23] Tonniger and colleagues[89]

Table 2 Early and late associations of S100 protein release after CPB

Early S100 protein release (from end of CPB to 5 h after CPB)	**Late S100 protein release (from 15 h to 48 h after CPB)**
(1) Age[43, 46, 87]	(1) Perioperative cerebral complications (stroke, delayed awakening and confusion)[5, 10, 41, 43]
(2) Duration of CPB[26, 46, 49, 93]	(2) Duration of circulatory arrest[5]
(3) Duration of aortic cross-clamping[3, 32]	(3) Duration of absent cerebral perfusion[5]
(4) Duration of circulatory arrest[5, 49]	(4) Patients with preoperative arteriosclerosis of the ascending aorta[43]
(5) Preoperative cerebrovascular complications (stroke, transient ischaemic attacks and arteriosclerosis of ascending aorta)[43]	(5) Neonates (until 15 h post-bypass)[49]
(6) Number of emboli especially during aortic cannulation[32]	
(7) Postoperative cerebral complications (stroke and confusion)[10]	
(8) Preoperative renal impairment (serum creatinine >177 µmol litre^{-1}), associated with increased serum S100 protein only at 5 h after CPB[43]	

found similar S100 protein levels after cold and warm bypass using the same CPB temperatures. S100 protein was measured 30 min after CPB in Tonniger's study,[89] which would probably not have detected the peak concentrations.

Jönsson and colleagues[43] characterized the S100 protein release pattern after CPB in 515 patients undergoing coronary artery bypass surgery, 85 (16.5%) of whom had pre-operative cerebrovascular disease. Samples were taken at the end of CPB, and after 5, 15 and 48 h. Serum levels of S100 protein decreased gradually with time after termination of CPB. An early increase in S100 protein at the end of CPB and up to 5 h was related to patient age (r=0.59, P<0.001;[87] r=0.29, P<0.0001[43]), and duration of CPB (r=0.89, P<0.001;[93] r=0.58, P<0.001;[49] r=0.93, P<0.001[26]). In addition, Jönsson and colleagues[43] found that patients with a previous history of stroke or transient ischaemic attack had higher S100 protein levels directly after CPB than patients who did not have such a history (mean (SD), 3.3 (2.4) *vs* 2.2 (1.8) µg litre^{-1}, P<0.001). Furthermore, patients with pre-operative impaired renal function (serum creatinine >177 µmol litre^{-1}) had higher S100 protein levels at 5 h after CPB.[43]

The relationship of increased levels of S100 soon after CPB to age suggests more cerebral vulnerability in older patients. Age is known to be a risk factor for increased neurological injury after cardiac operations,[37, 83, 90] and is the most important predictor of stroke following coronary artery bypass grafting surgery.[64] Interestingly, increased age has been found to predispose to impaired cognitive function after cardiac surgery.[63, 65] The most likely explanation is the increasing prevalence of arteriosclerosis with occult cerebrovascular disease as well as an increased risk of embolism from ascending aortic plaques in older patients.[9]

After cardiac surgery, most of the neurological injuries have been thought to be due to macroemboli (200 µm in diameter or greater) and microemboli (less than 200 µm in diameter).[12–14, 50, 60, 71, 74, 81] Macroemboli (associated with atherosclerotic plaque disruption) are believed to precipitate focal defects, whereas particulate microemboli (consisting of white cell and platelet aggregates, or fat) may be implicated in more subtle cerebral dysfunction.[52]

Patients with pre-existing cerebrovascular disease such as a past history of stroke, transient ischaemic attack or an atheromatous aorta, may have subclinical cerebral pathology, which predisposes to early S100 protein release after CPB.[43] In addition, patients with a previous history of cerebrovascular disease are generally believed to be at greater risk of further cerebral injury during CPB.[70] Primary perioperative cerebral complications such as delayed awakening, confusion or stroke are associated with higher levels of S100 protein at 15–48 h after CPB.[43]

Early release of serum S100 protein after CPB is associated with different pre- and perioperative events and it is difficult to determine the exact cause of its release (Table 2). The level of S100 protein at which stroke or any cerebral complication can be diagnosed is not entirely clear. In addition, the patterns of S100 protein release give little or no information about the anatomical distribution of the injury and its functional impact. However, it is generally considered an early indicator of brain injury that has occurred either during or after CPB. In particular, its value is that it can be measured at a time when other diagnostic techniques (e.g. neurological and neuropsychological examinations, CT scan, MRI) may not be suitable or are not able to detect such injuries.

Paediatric cardiac surgery

Serum S100 has been detected in neonates and in some younger children before CPB.[49] However, in children older than 8 yr, there were no detectable levels of S100 before CPB,[49] as in adult studies. The preoperative elevated serum level of S100 protein without obvious cerebral injury in children under 8 yr can possibly be explained by the less selective permeability of the blood–brain barrier combined with a higher protein turnover in the neuronal cells because of the rapidly maturing central nervous system.[49] A reduced renal excretion may also contribute to this increase of S100 in the youngest children.[49] The highest levels of serum S100 appeared directly after CPB followed by a decline, as in adult studies. This decline was not detected in neonates after circulatory arrest until 15 h after CPB,[49] which could indicate a continuous release of S100 protein into the serum of those patients (Table 2).

Table 3 Recommended S100 protein sampling times in patients undergoing cardiac surgery with CPB

(1) Pre CPB (basal)
(2) At the end of CPB (0 time)
(3) For studying early release pattern, samples should be taken at
  0 time (at the end of CPB)
  2 5 h after CPB
  5 h after CPB
(4) For studying the late release pattern, samples should be taken at:
  15 h after CPB
  24 h after CPB
  48 h after CPB

Recently, in neonates and infants undergoing open-heart surgery, Abdul-Khaliq and colleagues[1] found a significant and continuous increase of S100 protein compared with pre-bypass levels, at 5 min on CPB, and 5 min before and 5 min after aortic cross-clamping. Peak levels were reached at the end of CPB. Interestingly, they also recorded a concomitant elevation of malondialdehyde (a marker of radical-induced lipid peroxidation, which may provide information on excessive generation of free radical from membrane injury) parallel to the increased S100 protein, especially after declamping and at the end of CPB. An important pathogenic factor involved in the reperfusion injury is the generation of oxygen-free radicals.[8 27 59] Abdul-Khaliq and colleagues[1] suggested that injured astrocytes may release S100 protein, which penetrates the injured endothelial barrier and enters the blood. This assumption is supported by a simultaneous increase in malondialdehyde concentrations. Significant contamination of malondialdehyde from other organs is unlikely, because blood samples were from veins which drain the brain, and malondialdehyde only has a half-life of 10 min. The significance of such observations requires further neurophysiological and neurodevelopmental follow-up studies.

High serum levels of S100 protein have been associated with increased levels of the serum cytokine inflammatory mediators, interleukin 6 and 8 (IL-6 and IL-8). After paediatric cardiac surgery, IL-6 increased at the end of CPB and correlated with S100 at 2 h after CPB (r=0.55, P=0.03). IL-8 correlated with S100 protein at 24 h after CPB (r=0.77, P=0.002).[4] The authors suggested that increased S100 protein levels after cardiac surgery may, in part, be cytokine mediated.[4]

Thus, serial measurements of S100 protein with identification of early and late release patterns may, in the future, provide a marker for the more accurate diagnosis of cerebral injury after CPB. In addition, further studies need to be performed to identify the S100 protein release patterns after warm CPB in adults and children undergoing open-heart surgery.

The recommended timing for S100 protein estimation, when studying adult and paediatric patients undergoing cardiac surgery, is illustrated in Table 3.

S100 protein and neurological complications after cardiac surgery

Johnsson and colleagues[41] measured S100 protein and neurospecific enolase (NSE) levels in 35 patients, and found that elevated levels were associated with neurological complications after cardiac surgery. Samples for analysis were taken before the operation and on the second postoperative day. Eight patients (23%) suffered neurological complications after CPB, four (11%) had a stroke and four (11%) had diffuse non-focal encephalopathy. The patients who suffered neurological complications were older and had longer perfusion and aortic cross-clamp times. Also, patients undergoing intracardiac operations (valve surgery) with or without coronary bypass surgery had more neurological complications than patients who had CABG alone. The highest level of S100 was detected in a patient following aortic arch surgery who suffered a fatal stroke and died 9 days after surgery. Computed tomography (CT) performed after 6 days showed multiple large infarctions in both hemispheres[41] (Table 4). This suggests that the complexity of the operative procedure is an important risk factor for neurological complications after CPB surgery. However, patients who only underwent CABG had one-third of the risk of neurological complications compared to patients who underwent aortic aneurysm surgery or intracardiac operations with or without CABG (14% *vs* 36%, respectively).[41] Furthermore, Taggart and colleagues[86] confirmed that patients who underwent intracardiac operations had significantly higher serum levels of S100 after CPB than after CABG. One patient had a stroke on the first postoperative day after an intracardiac operation. Recently, Wolman and colleagues[94] in a multicentre study, also demonstrated that patients undergoing intracardiac surgery combined with CABG are at a greater risk of developing cerebral complications compared with CABG alone. They found a 2.5-fold increase (16% in combined intracardiac and CABG *vs* 6% in CABG alone) in both focal and diffuse cerebral complications. Interestingly, there was a fourfold increase in mortality (7.4% in combined intracardiac and CABG *vs* 1.9% in CABG alone) even in patients who did not sustain any cerebral injury. The causes of this difference were thought to be an increased risk of particulate and air emboli in open-chamber surgery, increased age, more associated disease, and longer CPB and aortic cross-clamp durations.[94] Thus, measurements of serum S100 protein during cardiac surgery will help in early identification of patients with an added risk of neurological complications after the operation.

In another study,[10] four patients developed cerebral complications after CPB surgery (Table 5), although patient 2 had a preoperative history of multiple strokes with persistent impairment of memory. His surgical procedure was complicated by prolonged CPB caused by haemorrhage. S100 protein was detected in his serum preoperatively and he had the highest level of S100 protein at

Table 4 Patients with perioperative stroke and levels of S100 protein after CPB surgery CPB, cardiopulmonary bypass, CABG, coronary artery bypass surgery; ICO, intracardiac operations CT, computed tomography; —, not measured

Study	No of patients	Type of operation	Type of CPB	Patients with postoperative stroke	S100 protein level (μg litre^{-1})				CT diagnosis of stroke
					After CPB	15 h after CPB	24 h after CPB	48 h after CPB	
(1) Astudillo[5]	10	Aortic arch surgery	Total circulatory arrest with retrograde cerebral perfusion	1	10.8	—	2.5	—	Several frontal cerebral infarctions
(2) Taggart[87]	40	ICO	Hypothermic CPB (28°C)	1	1.17	—	0.67	—	Left-sided infarction in the territory of left middle cerebral artery
	20	CABG		0					
(3) Jonsson[43]	515	CABG	Hypothermic CPB (28°C)	13	≈ 1.7 (median)	≈ 1.0 (median)	—	≈ 0.4 (median)	Not done
(4) Johnsson[41]	38	21 CABG, 2 aortic arch surgery and 15 (ICO ± CABG)	Mild to moderate hypothermia (30–32°C), deep hypothermia (15–18°C) with circulatory arrest for aortic arch surgery	Four patients had stroke					
				One with fatal stroke	—	—	—	9.5	Multiple large infarctions in both hemispheres
				Three with mild stroke	—	—	—	0.5–1.3 (range)	Not done
(5) Blomquist[10]	29	27 CABG, 2 ICO	Mild to moderate hypothermia (30–32°C)	1 (this patient had a history of preoperative stroke and complicated with postoperative stroke)	6.62	—	5.26	9.08	New areas of infarction in the temporal and frontal lobes

Table 5 S100 protein concentrations (μg litre^{-1}) in four patients with cerebral complications after CPB[10]

Patient no.	S100 protein concentrations (μg litre^{-1})				Cerebral complications
	Pre CPB	End of CPB	24 h	48 h	
1	0	3.2	0.5	0.2	Confusion
2	0.32	6.62	5.26	9.08	Infarction
3	0	8.7	1.6	0.5	Confusion
4	0	6.2	0.83	0.56	Confusion

48 h after surgery. The patient developed severe confusion and depression on the second postoperative day. A CT scan performed 4 days after surgery showed new areas of infarction localized in the temporal and frontal lobes (Table 4). In the other three patients with minor cerebral injuries, the highest levels of S100 protein were detected after CPB and decreased after 24–48 h, although they were still detectable (Table 5). In addition, in Astudillo and co-workers' study,[5] the patient with the highest S100 protein values after CPB and at 24 h after surgery developed a postoperative stroke. Several frontal cerebral infarctions appeared on CT after surgery (Table 4).

From the previous studies, it is clear that all patients with perioperative cerebral complications had increased levels of S100 after CPB surgery, except for one patient in Johnsson and co-workers' study[41] (Tables 4 and 5). This suggests that S100 protein is a sensitive marker for brain injury after CPB surgery. In patients with cerebral infarction confirmed by CT, elevated levels of serum S100 were sustained and increased with time, suggesting a progressive release of S100 into the circulation through disruption of the blood–brain barrier[10 41 42] (Tables 4 and 5). As the biological half-life for S100 is short, the serum concentration must be maintained by persistent release.

S100 protein and neuropsychological dysfunction after cardiac surgery

Grocott and colleagues[33] found an association between serum S100 protein level and neurocognitive dysfunction after CPB surgery. In addition, Kanbak and colleagues[44] found a moderate correlation (r=−0.43) between the Visual Aural Digit Span test (VADST) and serum S100 protein concentrations after CPB. Recently, Kilminster and colleagues[46] studied S100 protein release during and 5 h after the onset of CPB, and neuropsychological tests preoperatively and for 6–8 weeks after surgery in 130 patients undergoing cardiac surgery. They[46] found that less S100 protein release was associated with better neuropsychological performance, and the change in neuropsychological tests accounted for 23% of the variance of S100 protein area under the curve (AUC) release. With further experience, S100 protein may provide a prognostic indicator for patients with overt cerebral injury. However, the serum level of S100 protein gives no idea about the site or the clinical effects of any cerebral injury.

S100 protein release in patients without overt neurological dysfunction

High levels of S100 protein were recorded soon after CPB but decreased by 24 h postoperatively in between 11 and 87% of patients who recovered without overt neurological injury[5 10 41 43 87] (Table 6). Interestingly, early subtle cognitive dysfunction occurs in up to 70% of patients after CPB,[51] and it is associated with increased levels of S100 protein after CPB.[33 44 46]

An elevated level of serum S100 in patients with an uneventful clinical outcome might provide evidence of subclinical injury which may be due to diffuse microemboli and increased permeability of the blood–brain barrier, but not irreversible cerebral damage through neuronal ischaemia and death.[32 49 93]

Grocott and colleagues[32] confirmed the association between elevated levels of S100 after CPB and the number of middle cerebral artery microemboli detected by transcranial Doppler, especially those occurring during the period of aortic cannulation. In addition, Babin-Ebell and colleagues[7] observed that the release of S100 protein (calculated as AUC) was related to thrombin formation assessed by thrombin–antithrombin complex (TAT), and to the total embolus count (r=0.71, P=0.0001, and r=0.42, P=0.009, respectively) during cardiac surgery. The blood–brain barrier is based on the endothelial lining of the vasculature and, under normal circumstances, is not permeable to proteins.[28] The systemic inflammatory response syndrome and endothelial cell activation and injury are well known to occur after cardiac operations.[11 16] The endothelium leukocyte interaction with the release of inflammatory mediators leads to damage to endothelial integrity, sticking of leukocytes in the microcapillary bed and microcirculatory dysfunction.[49] The increased endothelial permeability of the blood–brain barrier could explain the augmented release of S100 protein in the blood after CPB.

Harris and colleagues[36] have shown that cardiac surgical patients investigated using MRI within 1 h of surgery all showed signs of brain oedema. None of the patients experienced any major neurological complications after CPB. Such oedema may be regarded as indicative of cytotoxic reactions or vasogenic disorders, both of which are known to compromise the blood–brain barrier.[73] Using MRI, cerebral pathology has been documented in 30% of patients without overt clinical signs after CPB.[88]

Table 6 Clinical outcome and serum level of S100 protein

Study	Number of patients (%) with normal serum level of S100	Number of patients (%) with pathological serum level of S100	Total
(1) Johnsson[41]			
neurological complications	1 (2.9%)	7 (20%)	8 (22.9%)
no complications	23 (65.7%)	4 (11.4%)	27 (77.1%)
total	24 (68.6%)	11 (31.4%)	35 (100%)
(2) Astudillo[5]			
neurological complications	0	2 (20%)	2 (20%)
no complications	0	8 (80%)	8 (80%)
total	0	10 (100%)	10 (100%)
(3) Jonsson[43]			
neurological complications	0 (0%)	42 (8.2%)	42 (8.2%)
no complications	24 (4.7%)	449 (87.1%)	473 (91.8%)
total	24 (4.7%)	491 (95.3%)	515 (100%)
(4) Taggart[87]			
neurological complications	0	1 (1.7%)	1 (1.7%)
no complications	12 (20%)	47 (78.3%)	59 (98.3%)
total	12 (20%)	48 (80%)	60 (100%)
(5) Blomquist[10]			
neurological complications	0 (0%)	4 (14.1%)	4 (14.1%)
no complications	5 (17%)	20 (68.9%) (14 at 12 h after CPB in first group and 6 at 10 h in the second group)	25 (85.9%)
total	5 (17%)	24 (83%)	29 (100%)

Table 7 Correlations of S100 protein levels after CPB and on the first postoperative day with the duration of CPB, circulatory arrest (CA) and with period of absent cerebral perfusion (APC).[5] Durations are expressed as median (range). Duration of absent cerebral perfusion=duration of circulatory arrest – duration of retrograde cerebral perfusion. CPB, cardiopulmonary bypass; NS, not significant

	Correlations of S100 protein	
	Directly after CPB	**On the first post-operative day**
Duration of CPB; 184 (121–386) min	r=0.66, NS	r=0.31, NS
Duration of CA, 50 (3–118) min	r=0.71, $P<0.01$	r=0.83, $P<0.01$
Duration of ACP, 26 (3–70) min	r=0.68, NS	r=0.88, $P<0.01$

S100 protein after CPB with deep circulatory arrest

Cerebral dysfunction after cardiac surgery and after reconstructive surgery involving the aortic arch in particular, is a major concern: it can lead to a very long and costly rehabilitation period. Serum S100 protein was evaluated in 10 adults before, during and after reconstructive surgery of the thoracic aorta with deep hypothermic arrest.[5]

Retrograde cerebral perfusion was used in eight out of the 10 patients. All patients had an increase in serum S100 protein levels immediately after CPB, followed by a decrease on the first day after surgery. The patient with the highest S100 values, both after CPB and 1 day after surgery, developed a postoperative stroke, which was verified as several frontal cerebral infarctions on CT (Table 4). There was a significant correlation with a linear relationship between the levels of S100 and the duration of circulatory arrest after CPB, with the highest correlation seen on the first postoperative day (Table 7). The duration of absent cerebral perfusion (the duration of circulatory arrest minus the duration of retrograde cerebral perfusion) correlated significantly with S100 protein level on the first postoperative day (Table 7). However, there was no significant correlation between the level of S100 protein either immediately after CPB or on the first postoperative day and the duration of CPB (Table 7). The highest correlation was seen on the first postoperative day, when the duration of absent cerebral perfusion was tested against serum levels of S100 protein. This indicates that the duration of absent cerebral perfusion and circulatory arrest are damaging to the brain, despite the use of protective deep hypothermia and partial retrograde cerebral perfusion. Furthermore, the highest correlation seen on the first postoperative day indicates the lasting effect of circulatory arrest and periods of absent cerebral perfusion on S100 protein release. Despite the lack of a significant correlation between the duration of CPB and serum levels of S100 protein, it is difficult to exclude the effect of CPB *per se* on S100 protein (Table 7). The lack of a significant correlation might be explained by the greater impact of the duration of circulatory arrest on the S100 protein level or by a much wider range in the duration of circulatory arrest than in the duration of CPB. In a preliminary study by Kumar and colleagues[48] of four groups of patients (Table 1), the highest level of S100 after CPB was found in patients who underwent aortic arch surgery with circulatory arrest.

Table 8 Number of patients with elevated serum S100 protein, with or without an arterial line filter after CPB.[86] CPB, cardiopulmonary bypass

	Number of patients with elevated serum S100 protein		
	1 h after CPB (skin closure)	5 h after CPB	24 h after CPB
Filter group	9/20	0/20	0/20
Non-filter group	14/20	4/20	4/20

Recently, in a paediatric study, it was found that patients who experienced the highest levels of S100 after CPB had had cardiac surgery with circulatory arrest.[4,49] The single highest value, 15 μg litre^{-1}, obtained 5 h after CPB, was reported in a 3-day-old child in whom epileptic seizures developed 24 h after CPB with hypothermic circulatory arrest.[49] These studies[4,5,49] suggest a damaging effect of total circulatory arrest on the brain during adult and paediatric cardiac surgery.

S100 protein and cerebroprotective innovations

Two randomized studies have been performed to examine the effect of different therapeutic strategies on S100 protein after CPB surgery. Taggart and colleagues[86] studied the level of S100 protein in 40 patients undergoing CABG using a membrane oxygenator. Patients were randomly allocated to have a 43-μm heparin-coated arterial line filter or no filtration. Both the magnitude and persistence of S100 protein release was less in the filter group after CPB (Table 8). S100 protein was elevated in both groups at skin closure after CPB (the median and interquartile range for the non-filter group was 0.3 (0–0.55) μg litre^{-1} compared to 0 (0–0.39) μg litre^{-1} in the filter group). In addition, S100 protein was still detected in four patients in the non-filter group at 5 and 24 h after CPB. By contrast, it was not detected in any patient in the filter group at the same time points (Table 8). This study showed the benefit of arterial line filtration during CPB in improving cerebral protection particularly in terms of S100 protein release. This improvement may be due to a reduction in embolic load in the arterial line filter group, as the level of S100 protein appears to be correlated with the number of microemboli during CPB.[32] Furthermore, Pugsley and colleagues[68] reported a reduction in the incidence of microemboli detected by transcranial Doppler sonography when a 40-μm arterial line filter was used with a bubble oxygenator. More importantly, this strategy resulted in a reduction in both neuropsychological deficits and neurological injury in the form of a lower incidence of drowsiness, incoordination, nystagmus and depressed reflexes 24 h after surgery in the filter group (eight out of 50 in the filter group *vs* 19 out of 50 in the non-filter group), following CPB.[68]

In the second study, Svenmarker and co-workers[85] randomly allocated 115 patients undergoing CABG to have perfusion using either a CPB circuit treated with covalent-bonded heparin or a normal system (control group). S100 protein increased in both groups after termination of CPB, though significantly more in the control group (mean (SEM) 1.3 (0.16) μg litre^{-1} *vs* 0.95 (0.12) μg litre^{-1} in the study group (P=0.009)). After 7 h, levels of S100 declined, but were still higher (P=0.04) in the control group. The values of S100 protein on the first and second postoperative days did not differ between groups. The number of patients with neurological impairment was lower in the study group than the control group: one compared to nine patients, respectively. It is clear that cerebral outcome is much better after using a covalent-bonded heparin-treated circuit for CPB, and this may be due to reduced complement activation and systemic inflammatory responses.[85] It is also clear that both arterial line filtration and a heparin-coated CPB circuit reduce, but do not eliminate, cerebral injury after CPB.

In the future, better strategies to reduce or eliminate the systemic inflammatory response during CPB need to be developed. Additionally, further studies to evaluate the effect of these strategies on S100 protein, neurological and neuropsychological outcome, need to be performed.

Conclusions

S100 protein can be considered an early marker of cerebral injury after CPB. As a marker for cerebral damage, it is possible that S100 protein will have the potential to differentiate between the benefits and adverse effects of different perfusion strategies (e.g. choice of temperature, pulsatility, pH management) and surgical techniques. Furthermore, it can be used for evaluating the therapeutic effects of neuroprotective drugs, and with further experience, as a prognostic tool for an already existing neurological injury.

References

1 Abdul-Khaliq H, Blasig IE, Baur MO, Hohlfeld M, Alexi-Meskhisvili V, Lange PE. Release of cerebral protein S100 into blood after reperfusion during cardiac operations in infants: is there a relation to oxygen radical induced lipid peroxidation? *J Thorac Cardiovasc Surg* 1999; **117**: 1027–8

2 Allore R, O'Hanlon D, Price R, *et al*. Gene encoding subunit of S100 protein is on chromosome 21: implications for Down syndrome. *Science* 1988; **239**: 1311–3

3 Asharaf S, Bhattacharya K, Zacharias S, Kaul P, Kay PH, Watterson KG. Serum S100β release after coronary artery bypass grafting: roller versus centrifugal pump. *Ann Thorac Surg* 1998; **66**: 1958–62

4 Ashraf S, Bhattacharya K, Tian Y, Watterson K. Cytokine and S100B levels in paediatric patients undergoing corrective cardiac surgery with or without total circulatory arrest. *Eur J Cardiothorac Surg* 1999; **16**. 32–7

5 Astudillo R, Van der Linden J, Radergan K, Hasson L-O, Åberg B. Elevated serum levels of S100 protein after deep hypothermic

arrest correlate with the duration of circulatory arrest *Eur J Cardiothorac Surg* 1996; **10**: 1107–13

6 Aurell A, Rosengren LE, Karlsson B, Olsson JE, Zbornikova V, Haglid KG. Determination of S100 and glial fibrillary acidic concentrations in cerebrospinal fluid after brain infarction. *Stroke* 1991; **22**: 1254–8

7 Babin-Ebell J, Misoph M, Mullges W, Neukam K, Reese J, Elert O. Intraoperative embolus formation during cardiopulmonary bypass affects the release of S100B. *Thorac Cardiovasc Surg* 1999; **47**: 166–9

8 Blasing IE, Grune T, Schonheit K, *et al.* 4-Hydroxynonenal, a novel indicator of lipid peroxidation for reperfusion injury of the myocardium. *Am J Physiol* 1995; **269**: H14–22

9 Blauth CI, Cosgrove DM, Webb BW, *et al.* Atheroembolism from the ascending aorta. *J Thorac Cardiovasc Surg* 1992; **103**: 1104–12

10 Blomquist S, Johnsson P, Luhrs C, *et al.* The appearance of S-100 protein in serum during and immediately after cardiopulmonary bypass surgery: a possible marker for cerebral injury. *J Cardiothorac Vasc Anesth* 1997; **11**: 699–703

11 Boyle EM, Pohlman TH, Johnson MC, Verrier ED. Endothelial cell injury in cardiovascular surgery: the systemic inflammatory response. *Ann Thorac Surg* 1997; **63**: 277–84

12 Breuer AC, Franco I, Marzewski D, Soto-Velasco J. Left ventricular thrombi seen by ventriculography are significant risk factor for stroke in open-heart surgery. *Ann Neurol* 1981; **10**: 103–4

13 Breuer AC, Furlan AJ, Hanson MR, *et al.* Central nervous system complications of coronary artery bypass graft surgery: prospective analysis of 421 patients. *Stroke* 1983; **14**: 682–7

14 Bull DA, Neumayer LA, Hunter GC, *et al.* Risk factors for stroke in patients undergoing coronary artery bypass grafting. *Cardiovasc Surg* 1993; **1**: 182–5

15 Buttener T, Weyers S, Postert T, Sprengelmeyer R, Kuhn W. S100 protein: serum marker of focal brain damage after ischemic territorial MCA infarction. *Stroke* 1997; **28**: 1961–5

16 Cremer J, Martin M, Redl H, *et al.* Systemic inflammatory response syndrome after cardiac operations. *Thorac Surg* 1996; **61**: 1714–20

17 Fano G, Biocca S, Fulle S, Mariggio MA, Belia S, Calissano P. The S100 protein: a protein family in search of a function. *Progress Neurobiol* 1995; **46**: 71–82

18 Fano G, Mariggio M, Angelella P, Antonica N, Fulle S, Calissano P. The S100 protein causes an increase of intracellular calcium and death of PC12 cells. *Neuroscience* 1993; **53**: 919–25

19 Fassbender K, Schmidt R, Schreiner A, *et al.* Leakage of brain-originated proteins in peripheral blood: temporal profile and diagnostic value in early ischemic stroke. *J Neurol Sci* 1997; **148**: 101–5

20 Fazeli MS, Errington ML, Dolphin AC, Bliss TVP. Extra cellular proteases and S100 protein in long term potentiation in the dentate gyrus of the anaesthetized rat. *Adv Exp Med Biol* 1990; **268**: 369–75

21 Gao F, Harris DN, Sapsed-Byrne S, Sharp S. Neurone-specific enolase and Sangtec 100 assays during cardiac surgery: Part I – the effects of heparin, protamine and propofol. *Perfusion* 1997; **12**: 163–5

22 Gao F, Harris DN, Sapsed-Byrne S, Sharp S. Neurone-specific enolase and Sangtec 100 assays during cardiac surgery. Part III – Does haemolysis affect their accuracy? *Perfusion* 1997; **12**: 171–7

23 Gao F, Harris DN, Sapsed-Byrne S, Wilson J. Sangtec 100 release with hypothermic and normothermic bypass. *Perfusion* 1997; **12**: 45–6

24 Gao F, Harris DN, Sapsed-Byrne S. Time course of neurone-specific enolase and S100 protein release during and after coronary artery bypass grafting. *Br J Anaesth* 1999; **82**: 266–7

25 Gardner TJ, Horneffer PJ, Manolio TA, *et al.* Stroke following coronary artery bypass grafting a ten year study. *Ann Thorac Surg* 1985; **40**: 574–81

26 Gazzolo D, Vinesi P, Geloso MC, *et al.* S100 protein in children subjected to cardiopulmonary bypass. *Clin Chem* 1998; **44**: 1058–60

27 Giese H, Mertsch K, Blasing IE. Effect of MK 801 and U83836E on a porcine brain capillary endothelial cell barrier hypoxia. *Neurosci Lett* 1995; **191**: 169–72

28 Gillinov AM, Davis EA, Curtis WE, *et al.* Cardiopulmonary bypass and the blood brain barrier: an experimental study. *J Thorac Cardiovasc Surg* 1991; **104**: 1110–5

29 Gott JP, Cooper WA, Schmidt FE, *et al.* Modifying risk of extracorporeal circulation: trial of four antiinflammatory strategies. *Ann Thorac Surg* 1998; **66**: 747–54

30 Grieco G, d'Hollosy M, Culliford AT, Jonas S. Evaluating neuroprotective agents for clinical anti-ischemic benefit using neurological and neuropsychological changes after cardiac surgery under cardiopulmonary bypass: methodological strategies and results of a double-blind, placebo-controlled trial of GM$_1$ ganglioside *Stroke* 1996; **27**: 858–74

31 Griffin WST, Stanley LC, Ling C, *et al.* *Brain* interleukin I and S100 protein immunoreactivity are elevated in Down syndrome and Alzheimer disease. *Proc Natl Acad Sci USA* 1989; **86**. 7611–5

32 Grocott HP, Croughwell ND, Amory DW, White WD, Kirchner JL, Newman MF. Cerebral emboli and serum S100β during cardiac operations. *Ann Thorac Surg* 1998; **65**: 1645–50

33 Grocott HP, Croughwell ND, Verkerk GC, *et al.* Serum S100B as a predictor of neurologic and neuropsychologic outcomes after cardiac surgery. *Anesth Analg* 1998; **86**: S65

34 Haglid K, Yang Q, Hamberger A, Bergman S, Widerberg A, Danielson N. S-100β stimulates neurite outgrowth in the rat sciatic nerve grafted with a cellular muscle transplants. *Brain Res* 1997; **753**: 196–201

35 Hardemark HG, Ericsson N, Kotwica Z, *et al.* S100 protein and neuron specific enolase in CSF after experimental traumatic or focal ischaemic brain damage. *J Neurosurg* 1989; **71**: 727–31

36 Harris DNF, Bailey SM, Smith PLC, Taylor KM, Oatridge A, Bydder GM. *Brain* swelling in first hour after coronary bypass surgery. *Lancet* 1993; **342**: 586–7

37 Heyer E, Delphinn E, Adams D. Cerebral dysfunction after cardiac operations in elderly patients. *Ann Thorac Surg* 1995; **60**: 1716–22

38 Ingebrigsten T, Rommer B, Kongstand P, Langbakk B. Increased serum concentrations of protein S100 after minor head injury: a biochemical serum marker with prognostic value. *J Neurosurg Psychiatry* 1995; **59**: 103–4

39 Isobe T, Takahsi K, Okuyama T. S100a protein is present in neurons of central and peripheral nervous tissue. *J Neurochem* 1984; **43**: 1494–6

40 Izumi Y, Roussel S, Pinard E, Seylaz J. Reduction of infarct volume by magnesium after middle cerebral artery occlusion in rats. *J Cereb Blood Flow Metab* 1991; **11**: 1025–30

41 Johnsson P. Lundqvist C, Lindgren A, Ferencz I, Alling C, Stahl E. Cerebral complications after cardiac surgery assessed by S-100 and NSE levels in blood. *J Cardiothorac Vasc Anesth* 1995; **9**: 694–9

42 Johnsson P. Markers of cerebral ischaemia after cardiac surgery. *J Cardiothorac Vasc Anesth* 1996; **10**. 120–6

43 Jönsson H. Johnsson P, Alling C, Westaby S, Blomquist S. Significance of serum S100 release after coronary artery bypass grafting. *Ann Thorac Surg* 1998; **65**: 1639–44

44 Kanbak M, Avci A, Yener F, Koramaz I, Aypar U. Cerebral injury assessed by S100β protein and neuropsychologic tests after coronary artery bypass surgery. *Br J Anaesth* 1999; **82**: (Suppl 1) A.292

45 Karpiak SE, Seroksz M, Rapport MM. Effects of antisera to S100 protein and to synaptic membrane function on maze performance and EEG. *Brain Res* 1976, **102**: 313–21

46 Kilminster S, Treasure T, McMillan T, Holt DW. Neuropsychological change and S100 protein release in 130 unselected patients undergoing cardiac surgery. *Stroke* 1999; **30**: 1869–74

47 Kornfeld DS, Zimberg S, Malm JR. Psychiatric complications of open-heart surgery. *N Engl J Med* 1965, **273**: 287–92

48 Kumar P, Dhital K, Hossein-Nia M, Patel S, Holt D, Treasure T. S-100 protein release in a range of cardiothoracic surgical procedures *J Thorac Cardiovasc Surg* 1997; **113**. 953–4

49 Lindberg L, Olsson AK, Anderson K, Jogi P. Serum S100 protein levels after pediatric cardiac operations: a possible new marker for postoperative cerebral injury. *J Thorac Cardiovasc Surg* 1998; **116**: 281–5

50 Lynn GM, Stefanko K, Reed III JF, Gee W, Nicholas G. Risk factors for stroke after coronary artery bypass. *J Thorac Cardiovasc Surg* 1992; **104**: 1518–23

51 Mahanna EP, Blumenthal JA, White WD, *et al* Defining neuropsychological dysfunction after coronary artery bypass grafting. *Ann Thorac Surg* 1996, **61**: 1342–7

52 Mangano DT, Mora Mangano CT. Perioperative stroke encephalopathy and CNS dysfuncton. *J Intensive Care Med* 1997; **12**. 148–60

53 Marinow MB, Harbaugh KS, Hoopes PJ, Pikus HJ, Harbaugh RE. Neuroprotective effects of preischemia intraarterial magnesium sulfate in reversible cerebral ischemia. *J Neurosurg* 1996; **85**. 117–24

54 Marshak DR, Peese SA, Stanley LC, Griffin WST. Increased S100β neurotrophic activity in Alzheimer's disease temporal lobe. *Neurobiol Aging* 1991; **13**: 1–7

55 Marshak DR, Pena LA. Potential role of S100 protein in Alzheimer's disease. an hypothesis involving mitotic protein kinase. *Prog Clin Biol Res* 1992, **379**: 289–307

56 McDonald JW, Silverstein FS, Johnston MV. Magnesium reduces *N*-methyl-D-aspartate (NMDA)-mediated brain injury in perinatal rats. *Neurosci Lett* 1990; **109**: 234–8

57 McIntosh TK, Vink R, Yamakami I, Faden AL Magnesium protects against neurological deficit after brain injury. *Brain Res* 1989; **482**: 252–60

58 McKhann GM, Goldsborough MA, Borowicz LMJ, *et al.* Predictors of stroke risk in coronary artery bypass patients. *Ann Thorac Surg* 1997; **63**. 516–21

59 Mertsch K, Grune T, Landhoff A, Saupe N, Siems WG, Blasig IE. Hypoxia and reoxygenation of the brain endothelial cells *in vitro*: a comparison of biological and morphological response. *Cell Mol Biol* 1995; **41**· 243–53

60 Mills SA Risk factors for cerebral injury and cardiac surgery. *Ann Thorac Surg* 1995, **59**: 1796–9

61 Missler U, Wiesmann M, Christine F, Kaps M S100 protein and neuron-specific enolase concentrations in blood as indicators of infarction volume and prognosis in acute ischemic stroke. *Stroke* 1997, **28**: 1956–60

62 Moore B. A soluble protein characteristic of the nervous system *Biochem Biophys Res Commun* 1965; **19**: 739–44

63 Newman M, Karmer D, Croughwell N, *et al.* Differential age effects of mean arterial pressure and rewarming on cognitive dysfunction after cardiac surgery *Anesth Analg* 1995; **81**: 236–42

64 Newman M, Wolman R, Kanchuger M, *et al.* Multicentre preoperative stroke risk index for patients undergoing coronary artery bypass surgery. *Circulation* 1996; **94**· (Suppl 2) 74–80

65 Newman MF, Croughwell ND, Blumenthal JA, *et al* Effect of aging on cerebral autoregulation during cardiopulmonary bypass association with postoperative cognitive dysfunction *Circulation* 1994; **90(part 2)**: II-243–II-49

66 Persson L, Hardemark H, Edner G, Ronne E, Mendel Hartving I, Pahlman S. S-100 protein in cerebrospinal fluid of patients with subarachnoid haemorrhage: a potential marker of brain damage. *Acta Neurochir* 1988; **93**: 116–22

67 Persson L, Hardemark HG, Gustafsson J, *et al.* S-100 protein and neuron-specific enolase in cerebrospinal fluid and serum. markers of cell damage in human central nervous system *Stroke* 1987; **18**: 911–8

68 Pugsley W, Klinger L, Paschalis C, Treasure T, Harrsion M, Newman S. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke* 1994, **25**: 1393–9

69 Pugsley W, Treasure T, Klinger L, Newman MF, Pascalis C, Harrison M. Microemboli and cerebral impairment during cardiac surgery. *Vasc Surg* 1990; **24**: 34–43

70 Redmond JM, Greene PS, Goldborough MA, *et al.* Neurologic injury in cardiac surgical patients with a history of stroke. *Ann Thorac Surg* 1996; **61**. 42–7

71 Roach GW, Kanchuger M, Mangano CM, *et al.* Adverse cerebral outcomes after coronary bypass surgery. *New Engl J Med* 1996; **335**: 1857–63

72 Rosén H, Rosengren L, Herlitz J, Blomstrand C. Increased serum levels of the S100 protein are associated with hypoxic brain damage after cardiac arrest. *Stroke* 1998, **29**. 473–7

73 Rowland LP, Fink ME, Rubin L. Cerebrospinal fluid blood-brain barrier, brain edema, and hydrocephalus. In: Kandel ER, Schwartz JH, Jessel TM, eds. *Principles of Neural Science*, East Norwalk, CT. Prentice-Hall, 1991; 1050–60

74 Sakakibara Y, Shiihara H, Terada Y, Ino T, Wanibuchi Y, Furuta S. Central nervous system damage following cardiopulmonary bypass surgery: a retrospective analysis of 1386 cases. *Jpn J Surg* 1991, **21**: 25–31

75 Sapsed-Byrne S, Gao F, Harris DN. Neurone-specific enolase and Sangtec 100 assays during cardiac surgery: Part II – Must samples be spun within 30 min? *Perfusion* 1997; **12**. 167–9

76 Scandinavian Stroke Study Group Multicenter trial of hemodilution in ischemic stroke: background and study protocol. *Stroke* 1985, **16**: 885–90

77 Selinfreund R, Bargar S, Pledger W, Van Eldik L Neurotrophic protein S100β stimulates glial cell proliferation. *Proc Natl Acad Sci USA* 1991; **88**: 3554–8

78 Shaw PJ, Bates D, Cartlidge NE, Heaviside D, Julian DG, Shaw DA. Early neurological complications of coronary artery bypass surgery. *BMJ* 1985; **291**: 1384–7

79 Shepard R, Simpson D, Sharp J. Energy equivalent pressure. *Arch Surg* 1966, **93**: 730–40

80 Singh AK, Bert AA, Feng WC, Rotenberg FA. *Stroke* during coronary bypass grafting using hypothermic versus normothermic perfusion. *Ann Thorac Surg* 1995; **59**: 84–9

81 Slogoff S, Girgis KZ, Keats AS Etiologic factors in neuropsychiatric complications associated with cardiopulmonary bypass. *Anesth Analg* 1982; **61**: 903–11

82 Stanley LC, Mark RE, Woody RC, *et al.* Glial cytokines as neuropathogenic factors in HIV infection. pathogenic similarities to Alzheimer's disease. *J Neuropathol Expt Neurol* 1994; **53**: 231–8

83 Stump DA, Newman SP, Coker LH, Wallenhaupt SL, Roy RC. The effect of age on neurologic outcome after cardiac surgery *Anesth Analg* 1992; **74**. S310

84 Stys PK, Ransom BR, Waxman SG. Effects of polyvalent cations and dihydropyridine calcium channel blockers on recovery of CNS white matter from anoxia. *Neurosci Lett* 1990; **115**: 293–9

85 Svenmarker S, Sandstrom E, Karlsson T, *et al.* Clinical effects of heparin coated surface in cardiopulmonary bypass. *Eur J Cardiothorac Surg* 1997; **11**: 957–64

86 Taggart DP, Bhattacharya K, Meston N, *et al.* Serum S100 protein concentration after cardiac surgery: a randomized trial of arterial line filtration. *Eur J Cardiothorac Surg* 1997; **11**: 645–9

87 Taggart DP, Mazel JW, Bhattacharya K, *et al.* Comparison of serum S100 beta levels during coronary artery bypass grafting and intracardiac operations. *Ann Thorac Surg* 1997; **63**: 492–6

88 Toner I, Peden CJ, Hamid SK, Newman S, Taylor KM, Smith PL. Magnetic resonance imaging and neuropsychological changes after coronary bypass graft surgery: preliminary findings. *J Neurosurg Anesth* 1994; **6**: 163–9

89 Tonninger W, Jandrasits O, Grimm M, Schmid R, Haider W, Grubhofer G. Comparison of S100 protein release during normothermic and mild hypothermic cardiopulmonary bypass. *Br J Anaesth* 1998; **80**: (Suppl 2) A.71

90 Tuman K, McCarthy RJ, Najafi H, Ivankovich AD. Differential effects of advanced age on neurologic and cardiac risks of coronary artery operations. *J Thorac Cardiovasc Surg* 1992; **104**: 1510–7

91 Usui A, Kato K, Abe T, *et al.* S100a0 protein in blood and urine during open-heart surgery. *Clin Chem* 1989; **35**: 1942–4

92 Waterloo K, Ingebrigtsen T, Rommer B. Neuropsychological function in patients with increased serum levels of protein S100 after minor head injury. *Acta Neurochir* 1997; **139**: 26–32

93 Westaby S, Johnsson P, Parry AJ, *et al.* Serum S100 protein, a potential marker for cerebral events during cardiopulmonary bypass. *Ann Thorac Surg* 1996; **61**: 88–92

94 Wolman RL, Nussmeier NA, Aggarwal A, *et al.* Cerebral injury after cardiac surgery; identification of a group at extraordinary risk. *Stroke* 1999; **30**: 514–22

95 Zimmer DB, Cornwall EH, Landar A, Song W. The S100 protein family: history, function, and expression. *Brain Res Bull* 1995; **37**: 417–29

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SHORT COMMUNICATIONS

Safety of patient-maintained propofol sedation using a target-controlled system in healthy volunteers†

J. A. C. Murdoch*, S. A. Grant and G. N. C. Kenny

University Department of Anaesthesia, Glasgow Royal Infirmary, 10 Alexandra Parade, Glasgow G31 2ER, UK

**Corresponding author: Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, North Carolina 27710, USA*

We investigated the safety of a patient-maintained system that allows individuals to operate a target-controlled infusion of propofol to achieve sedation. Ten healthy volunteers were recruited and instructed to try to anaesthetize themselves with the system. A target-controlled infusion of propofol was set to deliver a target propofol concentration of 1 μg ml^{-1}, and the subjects allowed to increase the target in increments of 0.2 μg ml^{-1} by pressing a control button twice in 1 s. There was a lockout time of 2 min and a maximum permitted target concentration of 3 μg ml^{-1}. Heart rate and pulse oximetry oxygen saturation (Sp_{O_2}) were monitored continuously, and non-invasive arterial pressure, ventilatory frequencies and sedation scores were measured every 5 min. Sedation was continued until the subject stopped pressing the button. A keyword was then read for the individual to remember and sedation discontinued. There were no instances of significant decrease of Sp_{O_2} or loss of airway control. Maximum target blood concentration of propofol recorded ranged from 1.4 to 3 μg ml^{-1}. Two subjects became oversedated, one of whom was unrousable with loss of eyelash reflex. No subject could recall the keyword, although one recognized it from a list of 10 words. We conclude that the patient-maintained sedation system described could not be guaranteed to produce only conscious sedation in all patients, and that close clinical supervision by an anaesthetist would still be required for safe operation.

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Patient-controlled sedation systems, which administer bolus doses of the agent, have been studied by other investigators and found to be both an effective[1] and popular[2] technique for patients undergoing surgery under regional anaesthesia. A patient-maintained sedation system, which delivers a target-controlled infusion of propofol, has also been used successfully to provide sedation for patients undergoing orthopaedic surgery,[3] and more recently as an anxiolytic premedication for patients undergoing day surgery.[4] With any system in which the patient has control of sedative administration, a major concern is safety, as regards the depth of sedation that can be achieved and the maintenance of cardiorespiratory function. The goal of any patient-controlled sedation system should be delivery of conscious sedation while operating safely to prevent oversedation. Ultimately this safety depends on the appropriateness of the staged increase in dose of the sedative drug, the effectiveness of the lockout interval in allowing equilibration of the drug with the effect site, and the ability of the subject to coordinate a successful push of the control button. These three elements should function together in a feedback loop to prevent oversedation in all situations, including that in which individuals might be determined to administer as much sedative as possible through repetitive operation of the control button. We aimed to test the feedback loop of our system, in such a situation, in healthy volunteers who were asked to operate the system repetitively in an attempt to anaesthetize themselves.

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Methods and results

Local Ethics Committee approval for the study and written informed consent were obtained from 10 healthy adult volunteers, aged 18–40 yr. The exclusion criteria were a history of intercurrent disease, cardiorespiratory, renal or hepatic dysfunction, psychiatric disorder or mental retardation, use of any medication with sedative effects or a history of anaesthetic problems. The experimental target-controlled infusion (TCI) system used for sedation consisted of a Graseby 3400 infusion pump, the rate of which was controlled by a backbar microprocessor programmed with pharmacokinetic data describing the distribution and elimination of propofol.[5] By entering the subject's age and weight, and the desired initial blood concentration of propofol, the system calculates the initial bolus and variable infusion rates to achieve and maintain this concentration as given by the pharmacokinetic model, and gives a calculated figure for 'effect site concentration'.[6] Connection of a control button to the backbar enables the subject to increase the target blood concentration (C_T) of propofol in increments of $0.2\ \mu g\ ml^{-1}$ by double pressing the button within 1 s. There is then a lockout period of 2 min during which no further increase is possible with a maximum attainable target concentration of $3\ \mu g\ ml^{-1}$. If no successful presses are detected for a period of 6 min, there is a stepped reduction in the target concentration to a minimum of $0.2\ \mu g\ ml^{-1}$.[3 4]

Before starting the sedation, the subjects were instructed in the use of the control button and allowed to get the feel of its operation. They were instructed to press the button as often as they could in an attempt to anaesthetize themselves. Measurement of non-invasive arterial pressure (NIBP), heart rate (HR), ventilatory frequency and pulse oximetry oxygen saturation (Sp_{O_2}) were recorded, and a 21G intravenous cannula sited. A target-controlled intravenous infusion of propofol (1% with lignocaine 20 mg per 50 ml) was started at an initial target concentration of $1\ \mu g\ ml^{-1}$, and time allowed for the calculated effect site concentration, as determined and displayed by the system,[6] to reach within $0.1\ \mu g\ ml^{-1}$ of the set blood target level. The control button was then activated and the subject reminded to double press it as often as possible. One further verbal encouragement to push the button was given during the study period if they failed to push it for more than 3 min.

Heart rate and Sp_{O_2} were monitored continuously, NIBP, ventilatory frequency and sedation score, using a modified Steward sedation score,[3] were measured every 5 min following the start of sedation. Sedation scores were assessed by one of the two authors, who were familiar with the assessment and scoring of sedation levels. Oversedation was defined as loss of response to verbal command. An Sp_{O_2} <94% or ventilatory frequency <8 were considered clinically significant and were to be treated with supplementary oxygen. A decrease in baseline NIBP or HR >30% or HR <50 min^{-1} were to be treated as considered appropriate by the investigator.

Table 1 Subject characteristics, sedation scores, maximum target concentrations (C_T) and dose of propofol and total sedation time. All values given as median (range) or number

Age	31 (23–40)
Weight (kg)	77.5 (57–86)
Sex (m . f)	9 : 1
Sedation scores when demands ceased:	**Number of subjects**
Consciousness .	
4 Fully awake	0
3 Lightly asleep, spontaneous eye opening	3
2 Eyes open on command	5
1 Responding to ear pinching	1
0 Unresponsive	1
Airway	
3 Opening mouth, cough on command	3
2 Clear unsupported airway	7
1 Airway obstructed on neck flexion only	0
0 Airway obstructed without support	0
Activity	
2 Raise arm on command	5
1 No purposeful movement	4
0 No movement	1
Maximum C_T propofol ($\mu g\ ml^{-1}$)	2.0 (1.4–3.0)
Time (min)	29.5 (9–46)
Dose of propofol ($\mu g\ kg^{-1}\ min^{-1}$)	88.3 (73.5–142.3)

Any sign of anaesthesia, such as loss of verbal contact or loss of eyelash reflex, was recorded. Sedation was discontinued if the subject became unresponsive or failed to double press the control button on three attempts or for a period of more than 3 min, if there was loss of airway control, pulse oximetry oxygen desaturation below 94% on room air, or the target concentration reached the maximum level of $3\ \mu g\ ml^{-1}$. This was the primary end point at which the deepest level of sedation achieved, the greatest predicted blood and corresponding 'effect site concentration' of propofol reached were recorded. At this time a keyword was read for the subject to remember. One hour after discontinuing the sedation, subjects were asked to repeat the keyword. If unable to do so a list of 10 words including the keyword was read out and again the subject was asked to identify it.

Ten healthy volunteers were recruited to the study. Subject characteristics are shown in Table 1. Maximum Steward sedation scores ranged from 2 to 8 with a median of 5, scores for consciousness, airway and activity at the maximum C_T propofol reached are shown in Table 1. Maximum C_T propofol reached ranged from 1.4 to $3.0\ \mu g\ ml^{-1}$ with a median of $2\ \mu g\ ml^{-1}$. The total dose of propofol administered ranged from 105 to 351 mg.

For seven of the subjects, the difference between maximum C_T propofol reached and the C_T at which the subject first failed to double press the control button were within $0.2\ \mu g\ ml^{-1}$ (equivalent to one successful press). Three of the subjects, who could not coordinate a double press, were still able to single press the control button at the maximum sedation. Two subjects did not respond to speech, and one was unrousable to painful stimulus, at 1.4 μg ml^{-1} with loss of eyelash reflex. There were no instances of significant decrease in Sp_{O_2} or loss of airway control.

No subject had automatic recall of the keyword, although one, whose lowest score for consciousness score was 3 at the maximum C_T propofol of 3 μg ml^{-1}, recognized it when it was read from the list.

Comment

Our system functioned to prevent oversedation in 80% of the subjects studied, all of whom were actively trying to anaesthetize themselves. For these individuals the feedback loop provided by the patient control button functioned well. The need to double press the button appeared to be an important safety factor for three individuals who could not coordinate a double press at maximum sedation level. However, two subjects became oversedated, with one displaying signs of anaesthesia. It is possible that our increments of C_T propofol 0.2 μg ml^{-1} and 2-min lockout time failed to provide an adequate feedback loop. Reducing the staged increments in target concentration, and so delivery dose, with each successful press and increasing lockout time could allow more complete equilibration of blood and effect site concentrations of propofol and, therefore, could reduce the incidence of oversedation.

Thorpe and colleagues[7] studied 100 patients who were asked to anaesthetize themselves with a system delivering boluses of propofol with no lockout period. They reported an 11% incidence of oversedation with 2% reaching unresponsiveness. The total doses of propofol that their patients self-administered varied over a fourfold range from 66 mg to 248 mg. The twofold range of maximum target concentrations reached by our volunteers is likely to be a combination of the error inherent in estimates of predicted blood propofol levels (pharmacokinetic variability) and the predictable variability in pharmacodynamic response to propofol, reinforcing the need for careful titration of sedation according to individual needs. This variability makes it difficult to design a foolproof system to prevent oversedation.

For our subjects the motivation to press the control button relied entirely on the initial instruction given and one reinforcement on their first failure. This repeat instruction was given in an attempt to mirror the clinical situation where individuals will respond to heightened stimulation by pressing the control button. However, for ethical reasons, it is clearly difficult to recreate such surgical conditions and we acknowledge that our subjects were not exposed to any real clinical stimulation.

It is interesting that none of the volunteers had spontaneous recall of keywords, indicating that all had reached an amnesic level of sedation. Implicit memory could account for the recognition of the keyword by one volunteer, although this could equally be a chance finding.

In conclusion, the fact that two individuals became oversedated, with one showing signs of anaesthesia, indicates that, in its existing form, the patient-maintained sedation system described could be not guaranteed to produce conscious sedation in 100% of subjects instructed to attempt to anaesthetize themselves. How accurately this would reflect real clinical use may be debated, but we must conclude that close clinical supervision by an anaesthetist would be required to operate this system safely. However, the blood concentration of propofol decreases rapidly when the drug infusion is discontinued which would allow rapid recovery to a state of conscious sedation for those individuals who were oversedated. Further investigations looking at the effects of altering incremental doses and lockout times on improvement of the feedback loop are warranted.

References

1 Grattidge P. Patient-controlled sedation using propofol in day surgery. *Anaesthesia* 1992; **47**: 683–85

2 Osborne GA, Rudkin GE, Jarvis DA, Young IG, Barlow J, Leppard PI. Intra-operative patient-controlled sedation and patient attitude to control. A crossover comparison of patient preference for patient-controlled propofol and propofol by continuous infusion. *Anaesthesia* 1994; **49**: 287–92

3 Irwin MG, Thompson N, Kenny GN. Patient maintained propofol sedation. Assessment of a target-controlled infusion system. *Anaesthesia* 1997; **52**: 525–30

4 Murdoch JAC, Kenny GNC. Patient-maintained propofol sedation as premedication in day-case surgery assessment of a target-controlled system. *Br J Anaesth* 1999; **82**: 429–31

5 White M, Kenny GN. Intravenous propofol anaesthesia using a computerised infusion system. *Anaesthesia* 1990, **45**: 204–9

6 White M, Schenkels MJ, Engbers FH, Vletter AA, Burm AG, Bovill JG, Kenny GN. Effect-site modelling of propofol using auditory evoked potentials *Br J Anaesth* 1999, **82**: 333–9

7 Thorpe SJ, Balakrishnan VR, Cook LB. The safety of patient-controlled sedation. *Anaesthesia* 1997; **52**: 1144–50

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Rapacuronium recovery characteristics and infusion requirements during inhalation *versus* propofol-based anaesthesia

W. Fu[1], K. W. Klein[1], P. F. White[1]*, J. W. Chiu[1], H. J. M. Lemmens[2], D. G. Whalley[3], D. R. Drover[2] and C. P. Greenberg[4]

[1]Department of Anesthesiology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [2]Stanford University, Stanford, CA, USA, [3]Cleveland Clinic Foundation, Cleveland, OH, USA, and [4]Columbia University, New York, NY, USA

**Corresponding author*

We examined the effect of four maintenance anaesthetics on the neuromuscular blocking activity and spontaneous recovery characteristics after a short-term infusion of rapacuronium. Eighty ASA I–III adult patients undergoing elective surgery were studied at four centres. Anaesthesia was induced with propofol 1.5–2.5 mg kg^{-1} and fentanyl 1–2 μg kg^{-1}, followed by a bolus of rapacuronium 1.5 mg kg^{-1}. The patients were randomized to receive either desflurane (2–4% end-tidal, ET), sevoflurane (0.75–1.5% ET), isoflurane (0.4–0.8% ET), or a propofol infusion (75–150 μg kg^{-1} min^{-1}) for maintenance of anaesthesia in combination with nitrous oxide (60–70%) in oxygen. When the first twitch (T_1) of a train-of-four stimulus (using the TOF Guard® accelerometer) returned to 5%, an infusion of rapacuronium was started at 3 mg kg^{-1} h^{-1} and adjusted to maintain T_1/T_0 at 10%. The duration of infusion lasted between 45 and 60 min, and the average infusion rates of rapacuronium were similar in all groups, ranging from 1.6 to 2.5 mg kg^{-1} h^{-1}. There were no significant differences among the groups in the times for T_1/T_0 to return to 25%, 75% or 90%, or for T_4/T_1 to return to 70% and 80% upon discontinuation of the infusion. When potent inhalation anaesthetics are used in clinically relevant concentrations for maintenance of anaesthesia, the neuromuscular recovery profile of rapacuronium administered as a variable-rate infusion for up to 1 h is similar to that found with a propofol-based anaesthetic technique.

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Keywords: neuromuscular block, rapacuronium; anaesthetics, volatile, desflurane; anaesthetics, volatile, sevoflurane; anaesthetics, volatile, isoflurane; anaesthetics i.v., propofol; monitoring, acceleromyography

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Rapacuronium (ORG 9487) is a new aminosteroidal non-depolarizing neuromuscular blocking drug which has a rapid onset and short duration of action following an i.v. bolus dose.[1] In a preliminary study, van den Broek and colleagues reported that when a short-term (1 h) infusion of rapacuronium was administered during isoflurane anaesthesia, its time course of recovery was altered from that of a short- to an intermediate-acting neuromuscular blocking drug.[2] However, there are a lack of data pertaining to the relative potentiating effect of different maintenance anaesthetics on rapacuronium-induced blockade.

Thus, we evaluated the neuromuscular blocking effects and spontaneous recovery profile when a continuous infusion of rapacuronium was administered during general anaesthesia maintained with equipotent concentrations of either desflurane, sevoflurane or isoflurane *versus* propofol in combination with nitrous oxide (N_2O).

Methods and results

After obtaining institutional review board approval and written informed consent, 80 ASA I–III patients aged between 18 and 70 yr, undergoing elective orthopaedic and general surgery procedures with an anticipated duration of at least 2 h, were enrolled at four United States medical centres. Exclusion criteria included clinically significant hepatic, renal or neuromuscular disease, pregnancy, anticipated difficult intubation, drug therapy known to modify neuromuscular blockade (e.g. anticonvulsants, aminoglycoside/polypeptide antibiotics) and those whose body weight was 30% above or below their ideal body weight. The

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investigation was designed as an open-label, parallel-group comparative, multicentre study in which patients were randomized in groups of 20 at each centre to receive either desflurane (n=5), sevoflurane (n=5), isoflurane (n=5) or propofol (n=5) in combination with nitrous oxide for maintenance of general anaesthesia.

Midazolam 1–3 mg i.v. was administered for premedication 10–15 min prior to induction of anaesthesia. Non-invasive blood pressure, electrocardiogram (ECG) and haemoglobin oxygen saturation (Sp_{O_2}) were monitored. Anaesthesia was induced with propofol 1.5–2.5 mg kg^{-1} and fentanyl 1–2 µg kg^{-1} i.v.. Mask ventilation with 100% oxygen was instituted while the baseline measurements of neuromuscular function were obtained using a TOF Guard® accelerometer (Organon Teknika NV, Belgium). The TOF Guard® electrodes, temperature thermistor-sensor and accelerometric transducer were positioned on the patient's arm prior to induction of anaesthesia, and the arm was carefully secured to the operating table armboard during the study period in order to obviate inadvertent movements which may produce artifactual readings. After obtaining a stable T_1 recording (baseline value), rapacuronium 1.5 mg kg^{-1} was injected over 5 s into a rapidly flowing peripheral i.v. line in the opposite arm. The patient was intubated within 90 s and mechanical ventilation was initiated to maintain the end-tidal (ET) carbon dioxide (CO_2) at 4.5–5.0 kPa.

Maintenance of anaesthesia consisted of either desflurane (2–4% ET), sevoflurane (0.75–1.5% ET), isoflurane (0.4–0.8% ET) or propofol infusion (75–150 µg kg^{-1} min^{-1}) in combination with 60–70% nitrous oxide in oxygen according to a computer-generated randomization scheme. The patients received fentanyl 1 µg kg^{-1} and/or labetalol 5–10 mg as needed to maintain haemodynamic stability. Central (oesophageal) and peripheral (axillary) temperatures were monitored and maintained above 36.5 °C and 32.5 °C, respectively, using a forced-air warming blanket. All patients received crystalloids (Plasmalyte®), with colloids or blood only administered if indicated.

When T_1/T_0 returned to 5%, a continuous infusion of rapacuronium was started at 3 mg kg^{-1} h^{-1} and adjusted to maintain T_1/T_0 at 10% for 45–60 min. After discontinuation of the rapacuronium infusion, the patients were allowed to recover spontaneously until the times for return of T_1/T_0 to 25%, 75% and 90%, as well as the times for return of T_4/T_1 to 70% and 80% were recorded, if clinically feasible. If the T_4/T_1 ratio was <70% at the end of surgery, a combination of neostigmine 50–70 µg kg^{-1} and glycopyrrolate 8–10 µg kg^{-1} was administered to reverse residual neuromuscular blockade.

Based on an earlier study involving a rocuronium infusion,[3] an *a priori* power analysis suggested that a sample size of 20 subjects per treatment group would provide at least 80% power for detecting a difference of one standard deviation in infusion rates between any two treatment groups at the P=0.05 significance level. The SAS (version 6.09) computer software package used for data analysis was run on a VMS operating system. Frequency and univariate procedures were used for summary statistics, and two-way analyses-of-variance using general linear models procedures were used for analysis of infusion rates and recovery variables. Data are presented as mean (SD), medians or numbers (Table 1), with P-values <0.05 considered statistically significant.

Although 80 patients were enrolled, five were excluded from the analysis because of protocol violations at the onset of the study, while subsequent violations precluded analysis of one patient who received the rapacuronium infusion for only 26 min and four patients who received additional anaesthetic agents before the end of the rapacuronium infusion. There were no significant differences in the patient characteristics (Table 1), rapacuronium infusion times (group means from 53 to 55 min), total rapacuronium dosages (group means from 3.4 to 3.9 mg kg^{-1}) and average rapacuronium maintenance infusion rates to maintain ~90% block (group means from 1.6 to 2.5 mg kg^{-1} h^{-1}) among the four anaesthetic groups. The maintenance dosages (MAC h^{-1}) of the potent inhalation agents were similar in the desflurane, sevoflurane and isoflurane groups. There were also no statistical differences in the times for T_1/T_0 recovery to 25%, 75% and 90%, or for T_4/T_1 to recover to 0.7 and 0.8 (Table 1).

Comment

In this study, the recovery times after discontinuing the infusion of rapacuronium were significantly longer than following a single intubating dose of rapacuronium.[1] These findings confirm a previous report which suggested that rapacuronium was altered from a short-acting to an intermediate-acting neuromuscular blocking drug when administered as an infusion.[2] The apparent pharmacodynamic change may be explained by the reduced contribution of distribution to plasma clearance, as well as the accumulation of the 3-desacetyl metabolite of rapacuronium (ORG 9488), which has a longer half-life and appears to be more potent than the parent compound.[4] Van den Broek and colleagues[2] demonstrated that a TOF ratio of 0.7 measured by mechanomyography (MMG) was attained 38 min after a 1 h infusion of rapacuronium, which was significantly shorter than the times reported in our study (71–92 min). This difference may be related in part to the less profound depth of neuromuscular blockade established in the earlier study (83% *versus* 92%, respectively), and the variations in recovery profiles as a result of using acceleromyography *versus* MMG monitoring.[5]

Desflurane, sevoflurane and isoflurane all potentiate the neuromuscular blockade produced by non-depolarizing neuromuscular blocking drugs,[6 7] whereas most studies have failed to demonstrate potentiation with propofol [8 9] We compared these potent inhalation anaesthetics to a propofol infusion for maintenance of anaesthesia and no statistically

Table 1 Physical characteristics, neuromuscular recovery and infusion rate data for the four study groups.* Data are expressed as means (SD), medians or numbers (*n*), age, range. ASA, American Society of Anesthesiologists, NA, non-applicable; MAC h^{-1}, sum of end-tidal concentration divided by the minimum alveolar concentration (MAC) value (adjusted for concomitant use of nitrous oxide and age) multiplied by the duration (h) at that concentration. Rapacuronium infusion rate = mean infusion rate of rapacuronium at 40 min after starting the maintenance infusion. Recovery index=time interval between recovery of T_1/T_0 to 25% and 75%. *There were no significant differences among the four study groups

	Desflurane	**Sevoflurane**	**Isoflurane**	**Propofol**
Age (yr)	51 (00–00)	50 (00–00)	47 (00–00)	53 (00–00)
Height (cm)	168 (11)	167 (12)	166 (10)	171 (9)
Weight (kg)	70 (15)	80 (20)	72 (16)	78 (20)
Sex (M/F)	16/4	15/5	14/6	16/4
ASA (I/II/III)	7/11/2	5/12/3	9/11/0	3/16/1
Potent inhaled anaesthetic (MAC h^{-1})	4.1 (2.5)	3.8 (2.1)	4.4 (2.2)	NA
Propofol infusion rate ($\mu g\ kg^{-1}\ min^{-1}$)	NA	NA	NA	119 (30)
Rapacuronium infusion rate ($mg\ kg^{-1}\ h^{-1}$)	2.3 (0.7) (2.4) (*n*=20)	1.6 (0.8) (1.7) (*n*=20)	2.5 (1.6) (2.4) (*n*=19)	2.2 (1.3) (2.3) (*n*=20)
Time (min) to				
$T_1/T_0 = 25\%$	15.3 (12.5) (10.3) (*n*=19)	19.9 (22.8) (12.0) (*n*=20)	13.3 (7.3) (13.2) (*n*=17)	10.5 (7.7) (7.8) (*n*=20)
$T_1/T_0 = 75\%$	35.6 (17.1) (28.2) (*n*=15)	55.7 (41.8) (44.4) (*n*=14)	44.1 (27.9) (36.1) (*n*=14)	32.6 (16.5) (25.8) (*n*=17)
$T_1/T_0 = 90\%$	39.5 (22.9) (30.8) (*n*=11)	73.3 (49.5) (79.2) (*n*=13)	60.1 (34.6) (56.6) (*n*=10)	37.5 (15.9) (32.3) (*n*=14)
$T_4/T_1 = 0.7$	73.0 (24.8) (79.9) (*n*=10)	106.7 (34.0) (115.4) (*n*=6)	85.0 (42.5) (82.8) (*n*=10)	70.6 (23.4) (68.5) (*n*=13)
$T_4/T_1 = 0.8$	83.4 (30.0) (84.0) (*n*=8)	139.5 (36.8) (130.5) (*n*=5)	85.4 (42.5) (70.9) (*n*=4)	82.1 (23.6) (85.6) (*n*=11)
Recovery index (min)	25.0 (14.3) (24.1) (*n*=15)	36.8 (28.6) (34.4) (*n*=14)	34.6 (24.0) (26.3) (*n*=14)	24.1 (15.0) (19.2) (*n*=17)

significant differences were found with respect to the recovery characteristics following an equi-effective rapacuronium infusion, although the mean values in the sevoflurane group did tend to be longer. These results are analogous to those of Wulf and colleagues[9] who demonstrated that spontaneous recovery of neuromuscular function following rocuronium was similar during propofol or volatile-based anaesthesia using a TOF Guard® monitor.

The failure to find any significant differences among the four anaesthetic techniques may be attributed to: (i) the limited sample sizes especially for the later recovery variables (due to the difficulty in accurately predicting the need for further muscle relaxation); (ii) the widespread disagreement in regard to comparative measurements with acceleromyography *versus* MMG or electromyography (EMG); and (iii) the inherent variability resulting from the fact that 20 patients were enrolled at each of four different medical centres. Most importantly, complete equilibration (steady-state conditions) for the anaesthetic agents[10] and rapacuronium between the muscle and plasma compartments may not have been achieved during the 45–60 min study period.

In conclusion, when potent inhalation agents are administered in clinically relevant concentrations for maintenance of anaesthesia, the neuromuscular blocking activity, recovery profile and infusion requirements for rapacuronium (administered as a variable-rate infusion) were similar to those observed during a propofol-based anaesthetic technique. Further studies are needed to validate these results using other neuromuscular monitoring techniques, a more tightly controlled propofol infusion rate and fixed ET concentrations of the inhaled agents.

Acknowledgement

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References

1 Wierda JMKH, van den Broek L, Proost JH, *et al.* Time course of action and endotracheal intubating conditions of ORG 9487, a new short-acting steroidal muscle relaxant; a comparison with succinylcholine. *Anesth Analg* 1993; **77**: 579–84

2 van den Broek L, Wierda JMKH, Smeulers NJ, *et al.* Pharmacodynamics and pharmacokinetics of an infusion of Org 9487, a new short-acting steroidal neuromuscular blocking agent. *Br J Anaesth* 1994; **73**: 331–5

3 Shanks CA, Fragen RJ, Ling D. Continuous intravenous infusion of rocuronium (ORG 9426) in patients receiving balanced, enflurane, or isoflurane anesthesia. *Anesthesiology* 1993, **78**: 649–51

4 Schiere SM, Proost JH, Wierda JMKH. Pharmacokinetics and pharmacokinetic-dynamic relationship between rapacuronium (Org 9487) and its 3-desacetylmetabolite (Org 9488). *Anesth Analg* 1999; **88**: 640–7

5 Nakata Y, Goto T, Saito H, *et al.* Comparison of acceleromyography and electromyography in vecuronium-induced neuromuscular blockade with xenon or sevoflurane anesthesia. *J Clin Anesth* 1998; **10**: 200–3

6 Vanlinthout LEH, Booij LHDJ, Vanegmond J, Robertson EN. Effect of isoflurane and sevoflurane on the magnitude and time course on neuromuscular block produced by vecuronium, pancuronium and atracurium. *Br J Anaesth* 1996; **76**: 389–95

7 Olkkola KT, Tammisto T. Quantifying the interaction of

rocuronium (Org 9426) with etomidate, fentanyl, midazolam, propofol, thiopental, and isoflurane using closed-looped feedback control of rocuronium infusion. *Anesth Analg* 1994; **78**: 691–6
8 Tran TV, Fiset P, Varin F. Pharmacokinetics and pharmacodynamics of cisatracurium after a short infusion in patients under propofol anesthesia *Anesth Analg* 1998; **87** 1158–63
9 Wulf H, Ledowski T, Linstedt U, *et al* Neuromuscular blocking effects of rocuronium during desflurane, isoflurane, and sevoflurane anaesthesia. *Can J Anaesth* 1998; **45**: 526–32
10 Hendrickx JFA, Soetens M, Van der Donck A, *et al.* Uptake of desflurane and isoflurane during closed-circuit anesthesia with spontaneous and controlled mechanical ventilation. *Anesth Analg* 1997; **84**: 413–8

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Which is most pungent: isoflurane, sevoflurane or desflurane?

M. F. TerRiet*, G. J. A. DeSouza, J. S. Jacobs, D. Young, M. C. Lewis, C. Herrington and M. I. Gold

Veterans Affairs Medical Center, Anesthesiology Service, University of Miami School of Medicine, Department of Anesthesiology, Miami, FL, USA

**Corresponding author: VA Medical Center (139), 1201 NW 16th Street, Miami, FL 33125, USA*

We compared the pungency and tolerability of three inhaled anaesthetics in a randomized, double-blind study. Eighty-one unpremedicated patients (n=27, each group) inhaled 2 MAC of isoflurane (2.3%), desflurane (12%) or sevoflurane (4%) for 60 s from an anaesthetic breathing circuit via a mask. Two blinded observers recorded coughing, complaints of burning and irritation, and how long the inhalation was tolerated. One sevoflurane patient coughed, but completed the study period, whereas 11 isoflurane patients and 20 desflurane patients coughed, objected verbally or removed the mask forcefully. All sevoflurane, 20 isoflurane and seven desflurane patients completed the study period (average 60, 49 and 33 s, respectively, $P<0.05$). The irritability grading was: desflurane > isoflurane > sevoflurane ($P<0.05$). Sevoflurane is the least irritating agent for inhalation at 2 MAC concentration.

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Keywords: coughing; anaesthetics, volatile, isoflurane; anaesthetics, volatile, sevoflurane; potency, anaesthetic, MAC; potency, anaesthetic, tolerance

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Volatile anaesthetics vary in their pungency. This limits their use for induction of anaesthesia. We assessed the acceptability of equally potent (2 MAC) inhaled concentrations of three commonly used volatile anaesthetic vapours.

Materials and methods

Eighty-one male patients, requiring or requesting general anaesthesia for their surgical procedure, were included in this randomized, double-blind investigation, approved by the institutional review board. Patients with signs of active or severe pulmonary disease were excluded. Smoking was not an exclusion criterion, unless patients were coughing frequently or were wheezing. No pre-medication was given. Standard monitoring and an intravenous infusion of a crystalloid solution were started. A table of random numbers was used to assign the anaesthetic vapour. One investigator (M.I.G.) primed the anaesthetic circuit and 3-litre reservoir bag with vapour and oxygen. To confirm the 2 MAC concentration in the circuit, a Datex Capnomac gas-analyser was used in addition to the Ohmeda respiratory gas monitor. Priming was considered to be complete when vapour concentrations were identical in both analysers (4%, 2.3% and 12% for sevoflurane, isoflurane and desflurane, respectively) and remained constant for at least 1 min. Two observers (M.T. and C.H.) were at the patient's side, blinded to treatment, vaporizers and gas-analysers.

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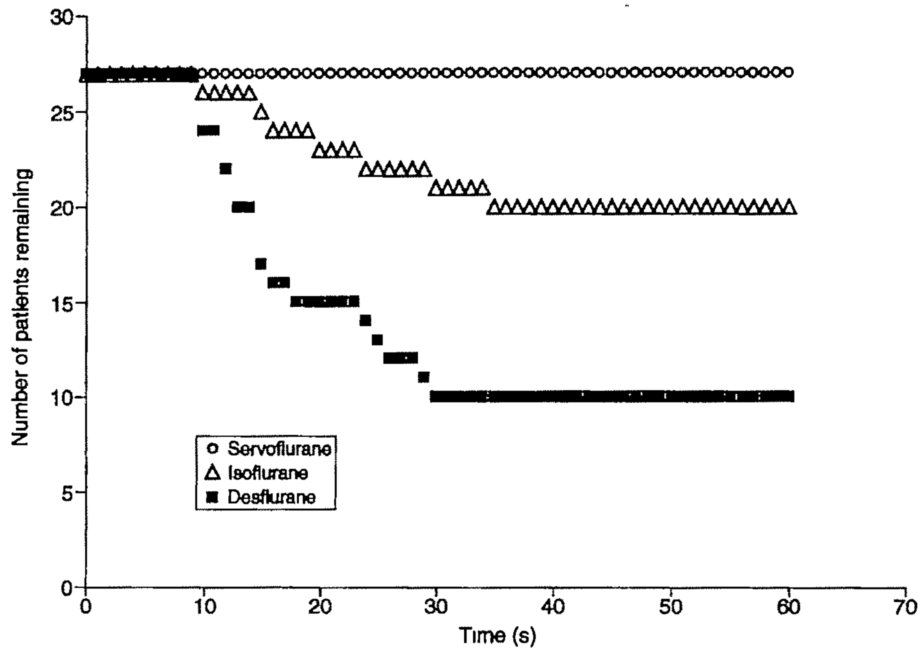

Fig 1 Patients who continue to breathe the anaesthetic versus time from the start of the inhalation

To ensure a leak-proof fit during the study and prevent potential entrainment of room air during the study period, a facemask was firmly applied to the patient's face. The patient was then instructed to exhale forcefully while the chimney-piece on the mask was occluded. If an air-leak existed around the mask, it was adjusted until no leak could be detected and held in place throughout the 60-s inhalation.

A Fink non-rebreathing valve[1] was used in this study to ensure a constant inspired concentration throughout the study period. It was attached in series to a three-directional valve leading to either room air or to the primed breathing circuit. At the start of the 60-s study period, the three-way valve was turned and the patient was instructed to take a single deep breath followed by normal breathing. The observers looked for signs of irritation, such as coughing, head movement or forceful removal of the mask by the patient. During the study period, the patient was asked whether he could continue or wanted the mask removed. The duration of time the inhalation was tolerated was measured by a stopwatch (C.H.). The study period ended when the patient expressed unbearable irritation, removed the mask, or after 60 s.

Statistical analysis

The chi-squared test was used to compare the responses to the three vapours. Analysis of variance was used to compare the time-of-tolerance. When the *F*-test of the analysis of variance was statistically significant, Bonferroni multiple comparison procedure was performed. A *P*-value less than 0.05 was considered statistically significant.

Results

There were no obvious systematic differences between the patients in the groups. Because this study was performed at a Veterans Affairs Hospital, all patients were male. The number of smokers in each group was similar (13 in the desflurane group, 14 in the isoflurane group and 14 in the sevoflurane group). No patient had a history of symptoms of COPD, asthma or other pulmonary disease.

One sevoflurane patient, 11 isoflurane patients and 20 desflurane patients coughed or objected overtly to inhaling the gas mixture ($P<0.05$). When questioned about burning, irritation or other discomfort, none of the sevoflurane patients complained, while 12 isoflurane and 21 desflurane patients did ($P<0.05$).

With time (seconds) as a variable, the means in all groups were also significantly different when compared with each other ($P<0.05$). Figure 1 shows how long patients tolerated the inhalation and how many completed the 60-s study period.

No correlation could be found between smoking history and reaction to the inhalation..

Discussion

A novel approach to rapid induction by mask is the inhalation of a single deep breath of high concentration of potent vapour. This 'vital capacity breath technique' has been investigated comparing sevoflurane and isoflurane,[2 3] as well as with sevoflurane and halothane[4] in adults. Sevoflurane not only acted more rapidly, but also produced an induction with a lower incidence of coughing and 'better patient acceptance'.[2,3,5] A different study compared the irritative qualities of four vapours at 1 and 2 MAC in volunteers.[6] Pungency was graded as isoflurane > enflurane > halothane > sevoflurane. Unfortunately, desflurane was not included in this comparison. It has the lowest blood–gas partition coefficient, but is associated with a high incidence of coughing and irritation.[7,8]

Our results show that during a 60-s inhalation of a 2 MAC concentration, sevoflurane is the least irritating anaesthetic agent. Isoflurane is more irritating than sevoflurane, but less so than desflurane, which seems to be unacceptably pungent. Most patients (20 out of 27) objected strongly to the inhalation.

A positive smoking history had no significant effect on the incidence of patient complaints. This may have been due to patient selection, as patients with respiratory symptoms were excluded from this study.

There are some limitations to our study. A 60-s time period was arbitrarily chosen, because we only sought to compare the initial irritability of the vapours. We think it is significant that some patients (seven receiving isoflurane, 20 receiving desflurane, respectively) did not tolerate even 60 s of exposure. We observed that very few patients lost consciousness after a single breath or within the 60-s time period. This needs further evaluation.

Second, the MAC concentration (and its multiple) represents equipotency based upon the response to a standardized surgical incision. It may not represent equipotency for airway irritability. Two MAC of desflurane should perhaps be compared with a higher concentration of isoflurane and sevoflurane. Equipotency in pungency remains conjectural.

Third, modern anaesthesia delivery systems use semi-closed circle systems, which may not be simulated exactly by a non-rebreathing valve. However, this valve allows delivery of only the anaesthetic mixture, the composition of which can be maintained precisely.[9,10] The purpose of its use was merely to deliver a constant anaesthetic concentration.

We conclude that, at the 2 MAC concentration, sevoflurane is significantly less irritating to the airways than isoflurane, and both are significantly less irritating than desflurane. Sevoflurane seems to be the best agent for rapid induction of general anaesthesia by mask.

References

1 Fink BR. A non-rebreathing valve of new design *Anesthesiology* 1954; **15**: 471–4

2 Yurino M, Kimura H. Vital capacity breath technique for rapid anaesthetic induction: comparison of sevoflurane and isoflurane *Anaesthesia* 1992; **47**: 946–9

3 Sloan MH, Conard PF, Karsunky PK, Gross JB Sevoflurane versus isoflurane induction and recovery characteristics with single-breath inhaled inductions of anesthesia. *Anesth Analg* 1996; **82**. 528–3

4 Yurino M, Kimura H. Vital capacity rapid inhalation induction technique: comparison of sevoflurane and halothane. *Can J Anaesth* 1993; **40**: 440–3

5 Lerman J, Sikich N, Kleinman S, Yentis S. The pharmacology of sevoflurane in infants and children *Anesthesiology* 1994; **80**. 814–24

6 Doi M, Ikeda K. Airway irritation produced by volatile anaesthetics during brief inhalation· comparison of halothane, enflurane, isoflurane and sevoflurane. *Can J Anaesth* 1993, **40**: 122–6

7 Jones RM. Desflurane and sevoflurane: Inhalation anaesthetics for this decade? *Br J Anaesth* 1990, **65**: 527–36

8 Taylor RH, Lerman J. Induction, maintenance and recovery characteristics of desflurane in infants and children. *Can J Anaest* 1992; **39**: 6–13

9 Dorsch JA, Dorsch SE. In: *Understanding Anesthesia Equipment*, 3rd edn. Baltimore: Williams and Wilkins, 1994, 226–30

10 Dripps RD, Eckenhoff JE, Vandam LD. In· *Introduction to Anesthesia*, 4th edn. Philadelphia: W.B. Saunders, 1972; 142

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Water vapour in a closed anaesthesia circuit reduces degradation/adsorption of halothane by dried soda lime

A. Schindler[1]*, M. Vorweg[2], T. W. L. Scheeren[1] and M. Doehn[2]

[1]*Departments of Experimental and Clinical Anaesthesiology, Heinrich-Heine-University, Moorenstr. 5, D-40225 Duesseldorf, Germany.* [2]*Department of Anaesthesiology, Merheim Hospital, Clinics of Cologne, Ostmerheimer Str. 200, D-51109 Cologne, Germany*

Dry lime causes a loss of volatile anaesthetics by degrading and adsorbing them. Degradation produces toxic substances and heat. Rehydration of lime stops degradation. If humidified breathing gases rehydrate lime, closed anaesthesia-circuits may reduce the loss of anaesthetics. To test this hypothesis we ventilated a reservoir bag with PhysioFlex®-devices using fresh (F) and dried (D) soda lime both in the presence (+H) and absence (–H) of halothane. We measured halothane delivery, humidity, temperature, and lime weight. Halothane was lost for 13 min in D+H. Humidity increased steeper with fresh lime, whereas absorbent weight increased more with dried lime; halothane increased both variables (F+H: 99%, 8 g; F–H: 93%, 6 g; D+H: 58%, 17 g; D–H: 24%, 15 g). Surprisingly, temperature remained constant, probably because of the high gas flow (70 litres min^{-1}) generated inside the Physioflex®. These findings indicate rehydration of dried lime by humid gases and a rapid cessation of the loss of halothane in the PhysioFlex®.

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Fresh carbon dioxide absorbents (soda lime and Baralyme®) contain about 12–17% of water.[1 2] Various situations result in unnoticed drying of lime[2 3] which may be harmful since dried lime degrades volatile anaesthetics to toxic products (e.g. carbon monoxide).[1 2] Additionally, degradation produces heat that may be deleterious to the airways.[2] Rehydration of dried lime abolishes these effects.[1 2]

Humidification of breathing gases, which is best in closed-circuits may lead to fast rehydration of dried lime. Therefore, we hypothesized that the PhysioFlex® closed-circuit anaesthesia machine reduces degradation of volatile anaesthetics by dried soda lime. This machine generates a high gas flow inside the circuit to homogenize the gas components and to prevent rebreathing of expired gas.[4] This gas flow may promote heat transfer from the absorbent to the patient, increasing the risk of airway injury. We also tested if, as assumed elsewhere,[1] the degradation of halothane liberates water.

Methods and results

To study how the loss of halothane from the PhysioFlex® is influenced by the lime's water content, we used either fresh (F+H, *n*=4) or dried (D+H, *n*=4) soda lime (Draegersorb 800, Draeger, Lübeck, Germany). It was dried by passing oxygen (10 litres min^{-1}) through an absorbent-packed cylinder until the repeatedly measured weight (scale type 16410; Maul, Bad König, Germany) of the cylinder was constant. Then, an oxygen flow of 1 litres min^{-1} was used to keep the lime dry.

The PhysioFlex® has been described in detail previously.[4] It is a closed-circuit anaesthesia machine that delivers the chosen volatile anaesthetic with end-expiratory anaesthetic concentration as the feedback-controlled variable. (With feedback control of the inspiratory concentration the machine works as a semi-closed circuit. This would have been inappropriate for our purpose.) Whenever the anaesthetic concentration (measured by infrared spectroscopy) is lower than set, liquid anaesthetic is injected into the circuit. Thus, the amount of anaesthetic that is necessary to reach and maintain the set concentration can be quantified. Because degradation and adsorption of the volatile anaesthetic will increase anaesthetic delivery by lowering the measured anaesthetic concentrations,[3] we expected a difference in anaesthetic delivery between our F+H- and D+H-experiments, i.e. a loss of anaesthetic from the gaseous phase of the system. As the PhysioFlex® removes surplus volatile anaesthetic in a built-in charcoal filter, we removed the charcoal to avoid interference with our measurements.

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The circuit was dried to 5–8% humidity during 2–3 h with siliceous earth, a strongly hygroscopic agent (Caesar & Lorentz, Hilden, Germany). From the start of the drying procedure until the end of each experiment, the PhysioFlex® ventilated a 3 litre reservoir bag (tidal volume 700 ml, respiratory rate 9 min^{-1}, positive end-expiratory pressure 0 cmH$_2$O, 30% oxygen in air).

After drying of the PhysioFlex®, we exchanged the siliceous earth with the absorbent sample to be studied without opening the circuit, took baseline measurements, and started carbon dioxide supply (200 ml min^{-1}). (The PhysioFlex® has two absorbent containers, one of which can be selectively bypassed. This allows the introduction of an absorbent sample without opening the circuit.) Carbon dioxide absorption contributes essentially to the rehydration of dried lime by producing water. Thereafter, we set an end-expiratory halothane concentration (Hal_{et}) of 2.0 vol% in the respective experiments and maintained this concentration until the end of the experiments (40 min). We measured continuously halothane delivery (PhysioFlex®), humidity, and temperature (Hygrotest 6200, Testotherm, Lenzkirch, Germany) inside the inspiratory limb of the circuit. Absorbent was weighed before and after each experiment.

All data are shown as median (range).

Substantial amounts of halothane were lost in the initial phase of the D+H experiments (stars in Fig. 1A). The median difference in the delivery of liquid halothane between D+H and F+H experiments was 1.96 ml after 6 min, peaked at 2.20 ml after 13 min and then decreased continuously to 1.59 ml. With D+H, the time to attain the set Hal_{et} was increased about 4-fold (D+H, 7 (6–9) min; F+H, 2 (1–2) min), the corresponding halothane dose was more than doubled (D+H, 3.9 (3.6–4.1) ml; F+H, 1.7 (1.2–1.7) ml) compared with F+H. However, to maintain Hal_{et} less halothane was delivered in the D+H experiments. Of note, the end of halothane loss coincided with humidity exceeding 20% during the D+H experiments. These findings indicate a substantial loss of halothane by dried lime in the initial minutes. However, about 30% (0.61 ml liquid halothane) of lost anaesthetic reappeared during the later course of the experiment.

These experiments were compared to experiments without halothane (F–H n=3; D–H, n=3) to determine if halothane influences the time course of the measured variables. The initial relative humidity and carbon dioxide supply was comparable in all experiments. We found considerable differences in the time course of humidity changes between the groups. Humidity increased steeply and approached 100% during the F experiments, whereas it remained below 70% (D+H) and 30% (D–H) after an initial decrease. The presence of halothane always accelerated humidification (Fig. 1B). The increase in absorbent weight was 17 (14–20) g for D+H, 15 (12–18) g for D–H, 8 (6–9) g for F+H and 6 (6–6) g for F–H. These results indicate that dried lime is rehydrated at the expense of humidification of the breathing gases and that water is liberated during degradation and/or adsorption of halothane. Temperature remained constant during all experiments.

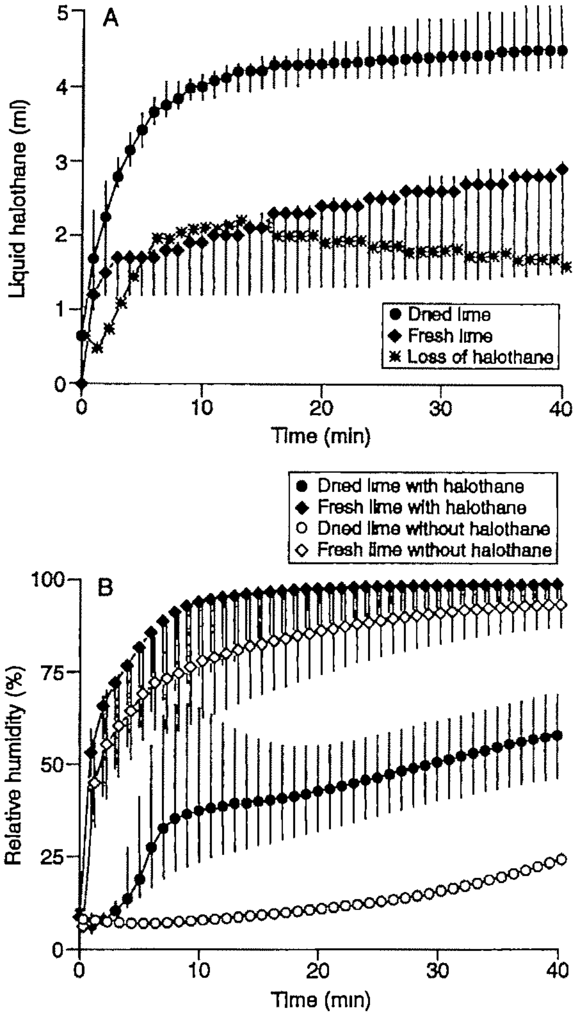

Fig 1 Time course of halothane delivery, loss of halothane and relative humidity inside the PhysioFlex®. Data presented as median (range) (A) Halothane delivery was considerably higher when dried lime (n=4) was used compared to fresh lime (n=4). The difference between fresh lime and dried lime experiments, i e the loss of halothane increased steeply during the first 6 min, peaked after 13 min and decreased again after this peak (B) Relative humidity increased much steeper when fresh lime was used (halothane, n=4, without halothane, n=3) than during the experiments with dried lime (halothane, n=4; without halothane, n=3) Note that the increase of humidity was preceded by a small decrease at the beginning of the experiments with dried lime. The presence of halothane increased relative humidity compared to experiments without halothane.

Comments

We have shown for the first time that the loss of halothane caused by dried soda lime ceases rapidly in the PhysioFlex® and that dried lime is rehydrated at the expense of the humidification of the breathing gases. Although degradation of halothane produces heat, temperature inside the inspiratory limb did not increase.

The loss of halothane which resulted from degradation and adsorption by dried soda lime[1,2,5,6] decreased by 0.61 ml after the 13th minute of our experiments without reaching a plateau (Fig. 1A). Thus, at least 27% of the lost anaesthetic was not degraded. It was first adsorbed in the molecular sieve of the dried lime and then replaced by water that rehydrated the absorbent.[1,3] Rehydration of dried lime by water vapour is generally possible, as proven by the increasing absorbent weight and initially decreasing humidity in our D+H and D–H experiments. The loss of halothane ceased more rapidly when humidity exceeded 20% and an initial humidity of 20% prevented any loss of halothane in similar experiments (data not shown). Thus, a relative humidity of 20% inside the circuit seems to prevent degradation of halothane and this threshold is rapidly reached in the PhysioFlex®. Hence, for the PhysioFlex® we can contradict the assumption that water vapour may not suffice to rehydrate dried lime during a short period.[1]

The decreasing loss of halothane could be explained if halothane concentration was overestimated due to overlapping infrared spectra of halothane and its degradation products. However, with 1.3 vol% of halothane upstream of an absorber filled with dry soda lime, infrared spectroscopy failed to detect halothane downstream of this absorber for more than 10 min,[3] excluding overlapping spectra. Moreover, if we had used isoflurane or enflurane, overlapping spectra may have been feigned and anaesthetic delivery would have differed less, because these two anaesthetics are degraded only partially.[6] Therefore, halothane was the best choice for our experiments. (None of the PhysioFlex® used in this study contained sevoflurane or desflurane.)

As discussed above, the cessation of the loss of halothane indicates that the degradation and adsorption of halothane are reduced at this time. In a semi-closed anaesthesia circuit carbon dioxide production peaked 10–15 min after dried Baralyme® started to degrade desflurane.[5] This time point also indicates a reduction in anaesthetic degradation. Therefore, degradation seems to be reduced twice as fast in the PhysioFlex® than in semi-closed circuits. One possible reason for this is the faster humidification of breathing gases in closed compared to semi-closed circuits, resulting in faster rehydration of dried lime.

Temperature remained constant inside the inspiratory limb of the circuit during our experiments. Thus, although degradation of volatile anaesthetics excessively produces heat[2,3] and although heat transfer could be promoted by the high internal gas flow inside the PhysioFlex®,[4] thermal injury of the patient's airway is unlikely to occur with this device. This is likely to occur as a result of the high gas flow cooling the lime and interrupting the vicious circle of a heat-boostered exothermic reaction.[1]

Baralyme® also degrades volatile anaesthetics, but it was not used because the two limes contain similar amounts of alkali hydroxides—the crucial components for degradation of volatile anaesthetics—and no qualitative differences between the two limes have been reported concerning anaesthetic degradation.[1] Thus, our results may predict the situation with Baralyme®.

In conclusion, dried soda lime causes a loss of halothane that ceases rapidly within the PhysioFlex® because of rapid humidification of the dried lime. Furthermore, thermal injury of the patient's airway is unlikely to occur with this device.

References

1 Fang ZX, Eger EI, Laster MJ, Chortkoff BS, Kandel L, Ionescu P. Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and Baralyme. *Anesth Analg* 1995; **80**: 1187–93

2 Baum J, Sitte T, Strauβ JM, Forst H, Zimmermann H, Kugler B. Die Reaktion von Sevofluran mit trockenem Atemkalk – Überlegungen anläβlich eines aktuellen Zwischenfalls. *Anasthesiol Intensivmed* 1998; **39**: 11–6

3 Stuttmann R, Knuttgen D, Muller M-R, Winkert AT, Doehn M. Halothanabsorption durch trockenen Atemkalk. *Anaesthesist* 1993; **42**: 157–61

4 Verkaalk APK, Erdmann W. Respiratory diagnostic possibilities during closed circuit anesthesia. *Acta Anaesth Belg* 1990; **41**: 177–88

5 Frink EJ, Nogami WM, Morgan SE, Salmon RC. High carboxyhemoglobin concentrations occur in swine during desflurane anesthesia in the presence of partially dried carbon dioxide absorbents. *Anesthesiology* 1997; **87**: 308–16

6 Strauss JM, Baum J, Sumpelmann R, Krohn S, Callies A. Zersetzung von Halothan, Enfluran und Isofluran an trockenem Atemkalk zu Kohlenmonoxid. *Anaesthesist* 1996; **45**: 798–801

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Randomized study of intravenous fluid preload before epidural analgesia during labour

S. M. Kinsella*, M. Pirlet[1], M. S. Mills[2], J. P. Tuckey[3] and T. A. Thomas

Sir Humphry Davy Department of Anaesthesia, St Michael's Hospital, Southwell Street, Bristol BS2 8EG, UK. [1]Department of Anaesthesia, Centre Universitaire de Santé de l'Estrie, 3001 12e Avenue Nord, Sherbrooke, Quebec, Canada J1H 5N4. [2]Department of Obstetrics and Gynaecology, St Michael's Hospital, Southwell Street, Bristol BS2 8EG. [3]Department of Anaesthesia, Royal United Hospital, Combe Park, Bath BA1 3NG, UK

**Corresponding author*

We performed a randomized controlled trial of the effect of intravenous fluid preload on maternal hypotension and fetal heart rate (FHR) changes in labour after the first epidural injection. Group 1 (49 women) received 1 litre of crystalloid preload. Group 2 (46 women) received no preload. No statistically significant difference was shown between the two groups for either of the outcomes. Hypotension was found in three women in group 1 and five in group 2 (P=0.4). Deterioration in FHR pattern was found in four women in group 1 and 11 in group 2 (P=0.08). This study has not shown a significant increase in the incidence of hypotension when intravenous preload is omitted before epidural analgesia using a low concentration of bupivacaine during labour. Because of the clinical importance of the difference in the rate of FHR deterioration between the two groups, we continue to administer preload for high-risk cases.

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In 1978, Collins and colleagues[1] demonstrated a significant reduction in maternal hypotension and fetal heart rate (FHR) changes when 1 litre of Hartmann's solution was given intravenously as a preload before epidural analgesia with bupivacaine 0.375%. Epidural analgesia is now usually initiated with weaker solutions of local anaesthetic, which may produce less hypotension, so preloading may be unnecessary. We have investigated this hypothesis.

Methods and results

The study was approved by the United Bristol Healthcare Trust Medical Ethics Committee. Healthy labouring women with a singleton cephalic fetus and cervical dilatation ≤8 cm and requesting epidural analgesia were eligible. Women with hypertension, body mass >100 kg or fetal distress were excluded.

The size of the study was based on that of Collins and colleagues,[1] who studied 104 women. We recruited 100 women. Verbal consent for the study was gained after informing the women about epidural analgesia.

Intravenous access was obtained using a 14 G cannula. Allocation to one of two groups was determined on the basis of a computer-generated list. In group 1, 1 litre of Hartmann's solution was infused rapidly before the epidural test dose. In group 2, the infusion was run at the slowest possible speed.

The cuff of an automatic blood pressure instrument (Dinamap; Johnson & Johnson, Ascot, UK) was placed on the left arm, and two baseline readings of systolic and diastolic pressure were taken between uterine contractions with the subject in the left lateral position. FHR was monitored continuously with an external ultrasonic transducer and recorded on a paper printout.

Fifteen millilitres of 0.1 or 0.2% bupivacaine containing fentanyl 50 μg was used to achieve analgesia. Bupivacaine 0.1% was usually used if the cervical dilatation was less than 5 cm, otherwise the 0.2% concentration was given. When the epidural catheter was in place, a test dose of either 8 ml of 0.1% or 4 ml of 0.2% solution was given. If there were no adverse effects after 5 min, the remainder of the 15 ml was injected. Blood pressure was measured between uterine contractions every 5 min for 30 min after the test

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Table 1 Hypotension and FHR changes after epidural compared with before the block was established. No significant differences were found when comparing group 1 *versus* group 2 or bupivacaine 0.1 *versus* 0.2%. (NB. If the FHR was abnormal before the epidural and after it, this would be registered as no change)

	Group 1: preload			**Group 2: no preload**		
Bupivacaine	**0.1%**	**0.2%**	**All**	**0.1%**	**0.2%**	**All**
No hypotension	31	15	46	24	17	41
Hypotension	2	1	3	3	2	5
Total	33	16	49	27	19	46
FHR						
Improved	0	0	0	1	0	1
No change	24	8	32	16	8	24
Deteriorated	2	2	4	7	4	11
Total	26	10	36	24	12	36

dose. If the woman turned over during this period, the blood-pressure cuff was transferred to the dependent arm.[2]

Hypotension was defined as a decrease, in the 30 min after the test dose, of greater than 20% from the lowest baseline systolic pressure. The baseline FHR trace was defined as the 30 min before the test dose, and FHR was then recorded for 60 min after the test dose. Traces were analysed and classified as normal, suspicious or abnormal, according to the scheme proposed by Steer and Danielian,[3] by an obstetrician (MSM) blinded to whether the patient had received preload.

Statistical analysis was performed using the Mann–Whitney test, the chi-squared test, Fisher's exact test or the *t*-test to compare physical and obstetric characteristics, the concentration of bupivacaine used, blood pressure changes and the FHR pattern. A probability of $P<0.05$ was taken as statistically significant.

Of the 100 women recruited, 51 were assigned to the preload group and 49 to the no-preload group. One woman from each group was excluded during the study. One had a placental abruption and Caesarean section, and the other delivered vaginally. One woman in group 1 and two in group 2 were excluded after completion of the study, as they were found to have had abnormal baseline FHR patterns before the epidural. Analysis was performed on a total of 49 women in the preload group and 46 in the no-preload group.

There was no difference in age, height, weight, parity and cervical dilation between the two groups. Hypotension occurred in three women in group 1 and five women in group 2 (Table 1; $P=0.4$). Hypotension was treated easily in all except for one woman in group 2. She had several episodes of hypotension for the first 40 min after starting the epidural despite treatment with 1.5 litre of Hartmann's solution and ephedrine 15 mg.

After the epidural, in group 1 the FHR pattern was normal in 32 women, suspicious in eight women and abnormal in one woman; in group 2 the FHR pattern was normal in 24 women, suspicious in 14 and abnormal in two. There were no differences between the two groups with respect to the number of parturients with suspicious or abnormal traces after the epidural ($P=0.21$).

FHR data were also investigated to detect any change from before to after the epidural. Deterioration occurred if a normal trace became suspicious or abnormal, or if a suspicious trace became abnormal. Data from both before and after the epidural were available for only 72 women. There was no statistically significant difference between the two groups in FHR deterioration (Table 1; $P=0.08$).

Hypotension and FHR deterioration occurred with similar frequencies in women who received 0.1 or 0.2% bupivacaine.

Discussion

Collins and colleagues showed a 2% incidence of hypotension in women who had a 1-litre preload versus 28% in a no-preload control group ($P=0.005$).[1] Using the same definition, we found hypotension in 6% of women who had a 1-litre preload and 10% of women with no preload. The difference between groups was not statistically significant. Although the investigator was not blinded as to which group the woman belonged to, the use of automated blood pressure recording in our study minimized observer bias.

A power analysis of our results showed that 1530 women would have had to be included in a study to determine whether preloading reduces hypotension, with a power of 0.9 and significance level of 0.05. Given that hypotension is infrequent, usually not severe and easily treated, such a study does not seem to be indicated.

Collins and colleagues[1] demonstrated a significant protective effect of preloading on the risk of FHR abnormalities after epidural. These occurred in 12% of preloaded women *versus* 34% with no preload. We did not show a statistically significant increase in the risk of a deterioration in FHR pattern when preloading was omitted. However, our proportion of cases (11 and 30%) was similar to that of Collins and colleagues.[1] Twenty-three women had FHR traces that were inadequate for interpretation, reducing the power of our trial to demonstrate a significant difference between the two groups. On the basis of our results, we would have to study 200 women to demonstrate a real difference in FHR deterioration with a power of 0.9 and significance of 0.05.

Early studies suggested a link between maternal hypotension after the use of labour epidurals and FHR abnormalities, but women were managed supine, leading to aortocaval compression.[4 5] More recently, Collins and colleagues[1] and Palmer and colleagues[6] did not find a relationship between hypotension and FHR abnormalities. Only one of the women in the present study who developed hypotension had a worsening FHR pattern.

The manner in which preloading might protect against FHR changes is not clear. Steiger and Nageotte[7] found that an increase in uterine baseline tone and contraction frequency after epidural analgesia, rather than hypotension, was associated with subsequent FHR abnormalities. As Cheek and colleagues[8] demonstrated a reduction in uterine contraction frequency after a 1-litre preload, the administration of a preload might balance a tendency towards an increase in contractility of the uterus after regional analgesia.

The clinical importance of the majority of FHR changes after epidural block is also uncertain. Although the method of FHR analysis used by Collins and colleagues[1] is not directly comparable with that which we used,[3] very few cases from either group in their study had unquestionably pathological features. We found only one abnormal trace in our preload group and two in the no-preload group. Spencer and colleagues[9] noted that the use of epidural analgesia was associated with an increased rate of FHR abnormalities, but not with fetal acidosis.

In summary, we found that omitting intravenous fluid loading before epidural analgesia in normotensive labouring women did not increase the incidence of hypotension significantly compared with women given a 1-litre preload. However, fluid administration before epidural may protect against FHR deterioration, possibly through a transient tocolytic action. Until further data are available, we suggest that intravenous preloading is used before epidural analgesia in labour when there is suspected or actual fetal compromise.

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References

1 Collins KM, Bevan DR, Beard DW. Fluid loading to reduce abnormalities of fetal heart rate and maternal hypotension during epidural analgesia in labour. *BMJ* 1978; **II**: 1460–1

2 Kinsella SM, Black AMS. Reporting of 'hypotension' after epidural analgesia during labour. Effect of choice of arm and timing of baseline readings. *Anaesthesia* 1998; **53**: 131–5

3 Steer PJ, Danielian PJ. Fetal distress in labor. In: James DK, Steer PJ, Weiner CP, Gonik B, eds. *High Risk Pregnancy: Management Options* London: W.B. Saunders, 1994; 1077–100

4 Schifrin BS. Fetal heart rate patterns following epidural anaesthesia and oxytocin infusion during labour. *J Obstet Gynaecol Br Commonw* 1972; **79**: 332–9

5 Wingate MB, Wingate L, Iffy L, Freundlich J, Gottsegen D. The effect of epidural analgesia upon fetal and neonatal status. *Am J Obstet Gynecol* 1974; **119**: 1101–6

6 Palmer CM, Maciulla JE, Cork RC, Nogami WM, Gossler K, Alves D. The incidence of fetal heart rate changes after intrathecal fentanyl labor analgesia. *Anesth Analg* 1999; **88**: 577–81

7 Steiger RM, Nageotte MP. Effect of uterine contractility and maternal hypotension on prolonged decelerations after bupivacaine epidural anesthesia. *Am J Obstet Gynecol* 1990; **163**: 808–12

8 Cheek TG, Samuels P, Miller F, Tobin M, Gutsche BB. Normal saline i.v. fluid load decreases uterine activity in active labour. *Br J Anaesth* 1996; **77**: 632–5

9 Spencer JAD, Koutsoukis M, Lee A. Fetal heart rate and neonatal condition related to epidural analgesia in women reaching the second stage of labour. *Eur J Obstet Gynecol Reprod Biol* 1991; **41**: 173–8

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Prospective evaluation of deep topical fornix nerve block *versus* peribulbar nerve block in patients undergoing cataract surgery using phacoemulsification

E. S. Aziz[1]* and A. Samra[2]

[1]*Department of Anaesthesia, Faculty of Medicine, Cairo University, 35A Abou Elfeda Street, Zamalek, Cairo, Egypt and* [2]*Department of Ophthalmology, Research Institute of Ophthalmology, Cairo, Egypt*

**Corresponding author*

We compared the efficacy of deep topical fornix nerve block anaesthesia (DTFNBA) *versus* peribulbar nerve block in patients undergoing cataract surgery using phacoemulsification. We studied 120 patients, allocated randomly to two groups. Group 1 (n=60) received peribulbar block with 5 ml of a 1:1 mixture of 0.5% plain bupivacaine and 2% lidocaine supplemented with hyaluronidase 300 i.u. ml^{-1}. Group 2 received DTFNBA with placement of a sponge soaked with 0.5% bupivacaine deep into the conjunctival fornices for 15 min. No sedation was given to either group. Analgesia was assessed by the reaction to insertion of the superior rectus suture and by questioning during the procedure. A three-point scoring system was used (no pain=0, discomfort=1, pain=2). Scoring was repeated at keratotomy, hydrodissection and hydrodelineation, phacoemulsification, irrigation and aspiration, and at intraocular lens insertion. If the patient's pain score was 0 or 1, no further action was taken. If the pain score at any stage of the operation was 2, intracameral injection of 1% preservative-free lidocaine was given. One patient in Group 2 needed intracameral lidocaine at the stage of phacoemulsification (P>0.05) and four experienced discomfort at irrigation and aspiration (P=0.043). We conclude that DTFNBA may be a useful needle-free anaesthetic technique in patients undergoing cataract surgery using phacoemulsification.

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General anaesthesia is hazardous in a large number of patients undergoing ophthalmic surgery, as many of them are elderly with multisystem disease. For diabetic patients, local anaesthesia is preferable as it reduces, to a great extent, the endocrine response to surgery.[1] Peribulbar block is becoming increasingly popular, as it is safer than retrobulbar block.[2] However, insertion of a needle near the eye is associated with the necessity to stop anticoagulant therapy, introduces the risk of retrobulbar bleeding and potential perforation of the globe. Such risks may necessitate the use of topical anaesthesia, although this is unusual. The use of deep topical fornix-applied nerve block anaesthesia has been reported in cataract surgery by Rosenthal.[3] It involves placement of local anaesthetic into the conjunctival fornices, from which the local anaesthetic diffuses across the conjunctiva into the peribulbar space and into the scleral nerves behind the eyes. In this study, we compared deep topical fornix nerve block anaesthesia (DTFNBA) with peribulbar nerve block in patients undergoing cataract surgery using phacoemulsification.

Methods and results

One hundred and twenty patients scheduled for elective intraocular surgery were enrolled in the study after we had obtained approval from the institutional ethics committee and patient consent. All patients had been assessed as suitable for a regional block technique and were unpremedicated. Patients were allocated randomly to one of two groups (closed envelope method). Group 1 (n=60) received peribulbar block. Group 2 (n=60) received DTFNBA.[3] The axial length (the distance from the cornea to the retina) is usually measured as part of the ophthalmic assessment using the axial length scanner. If the axial length is 26 mm or longer, the globe is elongated.[4] These patients were omitted from the study, as the risk of globe perforation if peribulbar block is used is greater.

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Before the block, a peripheral vein was cannulated and heart rate, oxygen saturation and non-invasive arterial blood pressure were monitored. In both groups, the conjunctival fornices were anaesthetized with local anaesthetic drops (oxybuprocaine 0.4%) before the block was started.

Peribulbar block was performed with a 5 ml syringe and a 25 gauge, 25 mm long disposable needle using a single inferotemporal injection[5 6] with 5 ml of a 1:1 mixture of 0.5% plain bupivacaine and 2% plain lidocaine supplemented with hyaluronidase 300 i.u. ml^{-1}. With the gaze fixed straight ahead in the primary position, the injection site was identified at the junction of the lateral one-third and medial two-thirds of the inferior orbital rim. The direction of the needle was slightly medial and cephalad. The local anaesthetic was injected slowly over a period of 1 min. DTFNBA was performed using two sponges (2×3 cm) soaked with 0.5% bupivacaine, applied deep into the conjunctival fornices.[3] The sponges were removed after 15 min. The surface anaesthetic effect was tested by grasping the limbus with Castroviejo 0.12 tissue forceps. A simple pain scoring system was used: no pain=0, discomfort=1, pain=2. The scoring was done at different stages of surgery: insertion of the superior rectus suture; keratotomy; hydrodissection and hydrodelineation; phacoemulsification; irrigation and aspiration; and intraocular lens insertion. If the pain score was 0 or 1, no further management was required. If the pain score was 2 at any stage of the operation, intracameral injection of 1% preservative-free lidocaine was given.

Parametric data were analysed using Student's *t*-test; non-parametric data were compared using the Mann–Whitney test. A P value of <0.05 was considered statistically significant.

There was no significant difference between the patient characteristics of the two groups (Table 1).

In Group 1, no patient experienced discomfort or pain at any stage of the operation. In Group 2, one patient experienced discomfort at the superior rectus suture, keratotomy, hydrodissection and hydrodelineation and phacoemulsification ($P>0.05$), and four patients experienced discomfort at irrigation and aspiration ($P=0.043$). At the stage of intraocular lens insertion, three patients in Group 2 experienced discomfort ($P>0.05$). In the only patient who experienced pain at the time of phacoemulsification, intracameral injection of 1% preservative-free lidocaine was applied.

The numbers of patients in each group with different pain scores at each stage of surgery are shown in Table 2.

Comment

Peribulbar block has gained popularity over the last few years, as it is safer than the traditional retrobulbar block.[2 4] In peribulbar block the needle tip remains outside the muscle cone, and thus the complications of retrobulbar block are avoided. However, peribulbar block has its own complications. Brain stem anaesthesia resulting from subarachnoid injection can occur if the peribulbar needle is inadvertently placed in the retrobulbar space. This is unlikely with a 25 gauge, 25 mm long needle. Extraocular muscle paresis can occur if local anaesthetic is injected directly into the muscle, or the needle may puncture a superficial vessel, causing conjunctival haemorrhage. The incidence of scleral perforation is higher with retrobulbar blocks. However, it has been reported with peribulbar block, especially if the axial length is more than 26 mm.[4] These

Table 1 Patient characteristics. Values are mean (SD) and age, range

	Group 1 Peribulbar block	Group 2 DTFNBA
Men/women	20/40	15/45
Age (yr)	74 (10)	75 (11)
Weight (kg)	64 (11.4)	60 (10.8)
ASA I	10	9
ASA II	30	31
ASA III	20	20

Table 2 Numbers of patients in relation to pain score at different stages of the operation. Data were analysed using the Mann–Whitney test *P = 0.043 between groups

	Group 1 Peribulbar block			Group 2 DTFNBA		
	No pain	Discomfort	Pain	No pain	Discomfort	Pain
Superior rectus suture	60	0	0	59	1	0
Keratotomy	60	0	0	59	1	0
Hydrodissection and hydrodelineation	60	0	0	59	1	0
Phacoemulsification	60	0	0	58	1	1
Irrigation and aspiration	60	0	0	56	4*	0
Intraocular lens insertion	60	0	0	57	3	0

complications are avoided with the use of DTFNBA, yet a good quality of analgesia is maintained. Rosenthal[3] has postulated that placement of local anaesthetic into the fornices allows absorption by the nerve trunks subserving the conjunctiva as they radiate across it. At the same time, by being absorbed posteriorly into the peribulbar space (and possibly transconally into the retrobulbar space), the posterior ciliary nerves, which supply the anterior sclera, anterior conjunctiva and limbus as well as the iris and ciliary body, are anaesthetized at their nerve roots.[3]

Each time a needle is introduced into the orbit there is a small but definite risk of complications. In this study, it has been shown that the use of DTFNBA offers analgesia comparable to that given by peribulbar block. Additional local analgesia may be required during lens irrigation and aspiration as there is significant patient discomfort at this stage of surgery. However, there is no akinesia with DTFNBA. This method is therefore not suitable for cataract surgery using extracapsular lens extraction; it is suitable only for surgery using phacoemulsification. The surgeon must be experienced with this type of surgery, as surgery is more difficult without akinesia. We conclude that DTFNBA is suitable for patients on anticoagulants and those who will not accept the use of injections around the eye. We recommend DTFNBA for patients undergoing cataract surgery using phacoemulsification.

References

1 Barker JP, Robinson PN, Vafidis GC, Hart GR, Sapsed-Byrne S, Hall GM. Local analgesia prevents the cortisol and glycaemic responses to cataract surgery. *Br J Anaesth* 1990; **64**: 442–5

2 Davis DB, Mandel MR. Posterior peribulbar block: an alternative to retrobulbar anaesthesia. *J Cataract Refract Surg* 1986; **12**: 182–5

3 Rosenthal KJ. Deep topical fornix nerve block anaesthesia. *J Cataract Refract Surg* 1995; **21**: 499–503

4 Duker JS, Belmon JB, Benson WE, *et al.* Inadvertent globe perforation during retrobulbar and peribulbar anaesthesia: patient characteristics, surgical management and visual outcome. *Ophthalmology* 1991; **98**: 519–26

5 Apel A, Woodward R. Single injection peribulbar local anaesthesia. *Aust NZ J Ophthal* 1991; **19**: 149–53

6 Aziz ES. Peribulbar block using a single inferotemporal injection technique with high dose hyaluronidase. *Egypt J Anaesth* 1997; **31**: 85–90

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BJA

CASE REPORTS

Implications of a tracheal bronchus for adult anaesthetic practice

I. D. Conacher

Department of Cardiothoracic Anaesthesia, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK

The problems posed by tracheal intubation in the presence of a tracheal bronchus in adults are exemplified with three case histories. The anomaly has been categorized into three types on the basis of its potential to cause problems when attempting intubation. Suggestions are given for ways of securing the airway that are safe and less likely to result in obstruction and hypoxia.

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The presence of a congenital anomaly of the central airway can be of significance to anaesthetists. The commonest anomaly is a tracheal bronchus that supplies the right upper lobe and which is reported to be present in 0.1–3% of the population.[1 2] In its most severe manifestation, a carina arises at mid-tracheal level. These usually present in childhood, sometimes surprisingly late, having been misdiagnosed as asthma, as the presenting symptoms may be wheeze or stridor. In adults, a variant is more common and is experienced as a spectrum of abnormalities ranging from a small but distinct bronchus connected to the lower third of the trachea to a bronchus that arises from the trachea at the level of the carina (carinal trifurcation) and just proximal to the normal origin of the right main bronchus. Arbitrarily, these have been classified as Types I, II and III (Fig. 1), for ease of description and significance to anaesthetists, and are illustrated here with individual case reports. Type I is largely of importance to those who may have to anaesthetize children; Type II abnormalities can potentially be obstructed by a normal tracheal tube; and Type III, similar to Type II, presents problems when one-lung ventilation (OLV), particularly of the right lung, is contemplated.

Case 1 (Type I)

In 1985, a 21-yr-old male presented for construction of an aorto-pulmonary window and re-anastomosis of collaterals to help relieve some of the hypoxia stemming from pulmonary atresia, an absent main pulmonary artery and a ventriculoseptal defect. A patent ductus arteriosus had mistakenly been tied off in infancy. He was cyanosed, with a dusky and plethoric complexion, had drumstick clubbing of the fingers, a haemoglobin concentration of 24 g dl^{-1}, and pulmonary function tests 50% of predicted. A history of wheeze with upper respiratory chest infections was not seen as particularly significant against the background of his general condition. Surgical access was planned through a right lateral thoracotomy: a medium-sized, left Robertshaw double-lumen tube (DLT) was inserted, and lung separation appeared to have been achieved. Thiopental, phenoperidine and pancuronium were used at induction and isoflurane and nitrous oxide for maintenance of anaesthesia. After the chest had been opened and OLV instituted, oxygen saturation, measured from interval blood gases, had decreased from 88 to 55% and was unchanged despite the use of 100% inspired oxygen. The DLT was removed and a tracheal tube inserted, with some improvement in oxygen saturation. At the end of the procedure, a rigid bronchoscope was inserted to remove secretions, at which point the abnormal anatomy of the airway was found. It appeared to be similar to that of a teenager who had been investigated for a respiratory wheeze and whose bronchogram is shown in Fig. 2.

Case 2 (Type II)

A 53-yr-old male ex-smoker presented with a shadow in the left lower lobe of the lung after a routine chest x-ray. It was proposed to insert a right-sided DLT prior to left thoracotomy but at pre-intubation rigid bronchoscopy a tracheal bronchus was noted 1 cm above the carina. It was felt that the tracheal limb of a DLT would block the tracheal bronchus and reduce the zones for ventilation significantly. A bronchial blocker (Rusch) was inserted through the rigid bronchoscope and sited in the left main bronchus. A 9.0 mm cuffed oral tracheal tube was placed beside the blocker so all zones of the right lung could be ventilated (Fig. 3).

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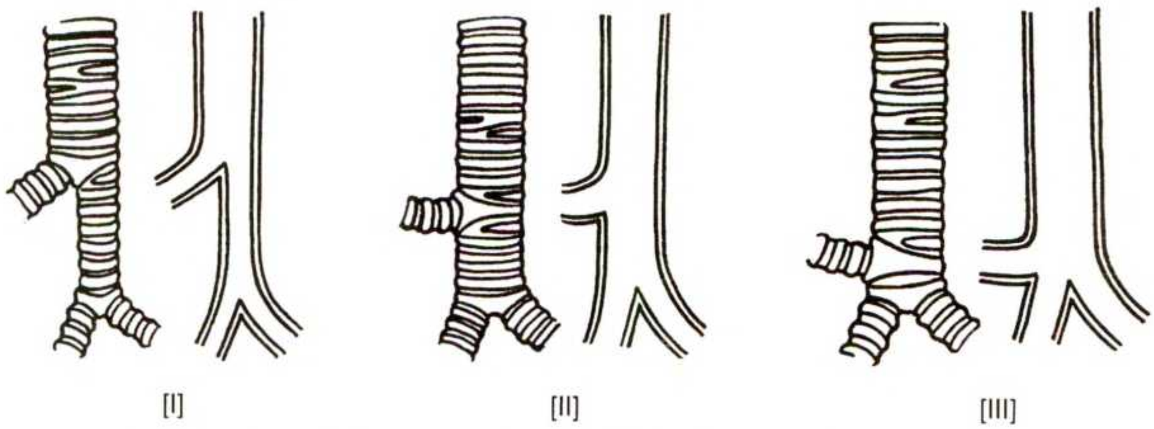

Fig 1 Schematic representation of the types of tracheal bronchus likely to be of significance to anaesthetists.

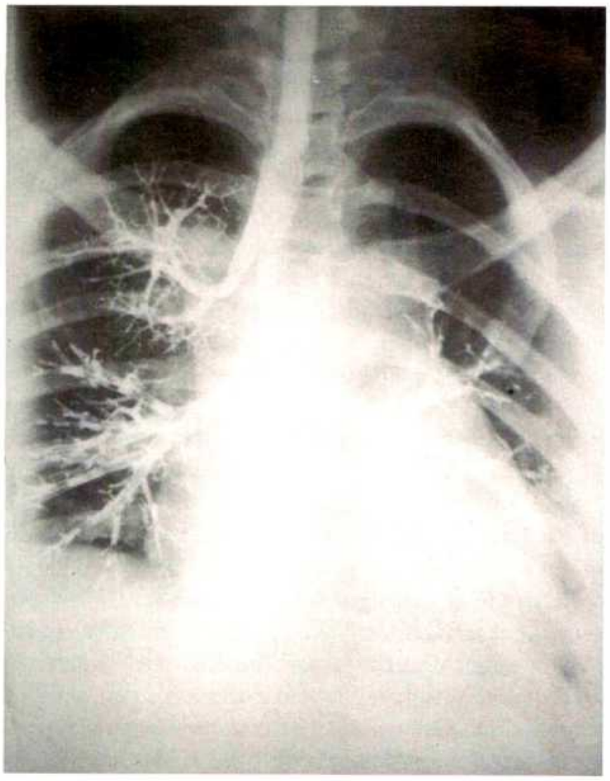

Fig 2 Bronchogram of a teenager who presented with a wheeze. The upper lobe (tracheal) bronchus can be seen arising just below the tip of a rigid bronchoscope close to the mid-tracheal point. The bifurcation at the level of a normal carina is between left main bronchus and bronchus intermedius to right middle and lower lobes.

Case 3 (Type III)

A 54-yr-old male with a secondary lesion from bowel malignancy in the left thorax was prepared for thoracotomy. At rigid bronchoscopy, a tracheal bronchus was noted at the level of the carina (Fig. 4). The chance that the bronchus would be blocked by the bronchial limb of a right-sided DLT was considered high so a blocker (Rusch) was inserted into the left main bronchus using a rigid bronchoscope. A 9.0 mm cuffed tracheal tube was used to ventilate the right lung.

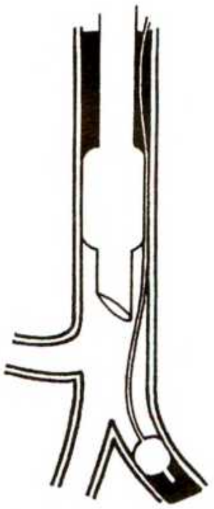

Fig 3 Schematic representation of the siting of a bronchus blocker and tracheal tube that prevents obstruction of a tracheal bronchus for OLV of the right lung.

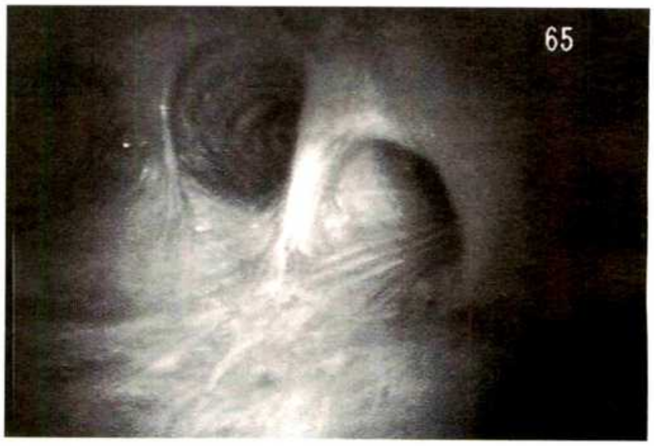

Fig 4 Carinal trifurcation. Clinical photograph at bronchoscopy. From left to right: main bronchus, carina; main bronchus; upper lobe carina; and upper lobe bronchus.

However, immediately before thoracotomy, and in searching for CT evidence of the tracheal bronchus, it was noted on a more recent CT scan that a further lesion was present in the right lung. It was felt that a sternotomy would be appropriate but there was no consent. The following day, a sternotomy was conducted and a left-sided DLT was used successfully to produce lung separation. Particular care was taken to ensure that there was a sufficient margin of safety[3] to ensure that the tracheal bronchus was not blocked by the tracheal lumen of the DLT or by herniation of the bronchial cuff.

Discussion

It is impossible, in Case 1, to know with any degree of certainty where the DLT lumen tube was placed. There are several possibilities, including correct siting and siting at the level of the tracheal bronchus with the true trachea cannulated with the endobronchial limb of the DLT. With hindsight, the hypoxia was most likely exacerbated by the fact that the patient did not have the pulmonary reserve nor the collateral oxygenating circulation to tolerate OLV. Nevertheless, the case illustrates the confusion caused by and the dangers of being unaware of the presence of a tracheal bronchus and the potential for a vital bronchus to be obstructed by a tracheal tube. An association of this type of anatomy with other congenital anomalies is known but the presence of cyanotic heart disease in this case distracted from the alerting symptom of a wheeze. Stridor is a typical presentation of severe manifestations of a tracheal bronchus. McLaughlin and colleagues[1] discussed the presentation, diagnosis and management of such cases, which can include surgical resection. However, it is probable that the bulk of these abnormalities are of incidental interest and of no prognostic significance, unless tracheal intubation is required. The child illustrated in Figure 2 was asymptomatic otherwise and needed no further immediate management once it was recognized that the wheeze was not indicative of asthma.

Longer survival of many of these patients with severe malformations may mean that a tracheal bronchus of this type is potentially more likely to be found in the adult population requiring tracheal intubation. Figure 2 shows the nature of the problem. Essentially, the appearance on bronchoscopy was of the main carina arising at or near the mid-trachea. The rest of the trachea looked as though it arose from what in the normal subject is the origin of the left main bronchus. The lower carina is a bifurcation of left main bronchus and bronchus intermedius and is sited at the usual level. It is only with radiological techniques, such as bronchography, that the true anatomy can be defined. Under normal circumstances, without this knowledge, it is easy to envisage that tracheal intubation could have several consequences, some of which would result in hypoxia. Either the tracheal bronchus or the true trachea could be entered by an uncut tracheal tube or one cut by design not to be placed beyond the mid-tracheal point. Cannulation of the tracheal bronchus would obstruct most of the rest of the respiratory system; cannulation of the true trachea would bypass the right upper lobe. The suggested management of the airway for anaesthesia for non-thoracic procedures includes the use of short tubes sited in the upper trachea, careful attention to the position of the tip of the tube, and fibre-optic confirmation that the tracheal bronchus is not obstructed.[2 4]

Case 2 proved to be a problem because of the nature of the surgery, and the solution to securing the airway was essentially related to the requirement for OLV. It has been used for the purpose of defining a Type II problem and is reported because it is illustrative of the potential dangers of tracheal tubes for the unwary in patients who have all the appearances of being normal. Such bronchial offsets have been reported as much as 6 cm from the carina,[2] in which case it is possible to envisage an anaesthetist inadvertently obstructing a tracheal bronchus and creating a hypoxic shunt with a tracheal tube of standard length.

Occasionally, a tracheal bronchus can be seen by examination of the tracheal wall on a chest x-ray,[2] but in practice these anomalies may come to light only accidentally. If an event occurs that makes the anaesthetist suspect that a tracheal bronchus is obstructed by a tracheal tube, it is likely that the only way of detecting it is by carefully withdrawing the tube to see if oxygen saturation is improved or by auscultation of the apical zone of the lung while such a manoeuvre is conducted. Although very rare, the condition should be added to main bronchial cannulation on a list of differential causes of desaturation associated with the action of tracheal intubation.

Type III anomalies (Case 3), sometimes described as carinal trifurcation, present particular problems for those using DLT.[5 6] In 20 yr of thoracic practice, the proposed airway management has had to be altered to cater for the presence of a tracheal bronchus in three further cases. This experience alone may not justify routine bronchoscopy (rigid or fibre-optic) prior to the use of blockers, endobronchial tubes and DLT, but the potential to confuse intubators and harm patients if the presence of one of these anomalies is undetected is reason enough to reinforce it as sensible practice before insertion of any form of lung separator. In some cases a DLT will function adequately to secure lung separation, but the use of a bronchus blocker and a standard tracheal tube has proved the most suitable way of delivering operating conditions that do not inconvenience the surgical operator and of securing safe and optimal OLV.

Acknowledgement

I am grateful to SODA David Crawford for the preparation of the artwork

References

1 McLaughlin FJ, Strieder DJ, Harris GB, Vawter GP, Eraklis AJ. Tracheal bronchus: association with respiratory morbidity in childhood. *J Pediatr* 1985; **106**: 751–5
2 Ikeno S, Mitsuhata H, Saito K, Hirabayashi Y, Akazawa S, Kasuda H. Airway management for patients with a tracheal bronchus. *Br J Anaesth* 1996; **76**: 573–5
3 Benumof J, Partridge BL, Salvatierra C, *et al.* Margin of safety in positioning modern double lumen tubes. *Anesthesiology* 1987; **67**: 729–38
4 Vredevoe LA, Brechner T, Moy P. Obstruction of anomalous tracheal bronchus with endotracheal intubation. *Anesthesiology* 1981; **55**: 581–3
5 Brodsky JB, Mark JBD. Bilateral upper lobe obstruction from a single lumen double-lumen tube. *Anesthesiology* 1991; **74**: 1163–4
6 Stene R, Rose M, Weinger MB, Benumof JL, Harrell J. Bronchial trifurcation at the carina complicating use of a double-lumen tracheal tube. *Anesthesiology* 1994; **89**: 1162–4

British Journal of Anaesthesia 85 (2) 320–1 (2000)

Sevoflurane and mivacurium in a patient with Huntington's chorea

P. Nagele* and A. F. Hammerle

Department of Anaesthesiology and General Intensive Care, General Hospital, University of Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria

**Corresponding author*

There is little experience of anaesthesia for patients with Huntington's chorea. These patients have an increased risk of intraoperative complications such as pulmonary aspiration. We present the successful anaesthetic management of a 17-yr-old patient suffering from Huntington's chorea requiring urgent appendectomy. After rapid-sequence induction with thiopental 400 mg and succinylcholine 100 mg, anaesthesia was maintained with sevoflurane. For maintenance of neuromuscular blockade mivacurium 10 mg was administered and repeated 15 min later. Except for a short episode of postoperative shivering, the perioperative course was uneventful. Sevoflurane and mivacurium were used safely and effectively in this patient.

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Only a few case reports exist concerning the anaesthetic management of patients suffering from Huntington's chorea.[1–9] Huntington's chorea is a rare hereditary disorder of the nervous system. Symptoms usually appear between the ages of 30 and 45 yr and include choreatic movements, progressive mental deterioration and ataxia. Early onset of symptoms is associated with more rapid and severe progression of the disease. Patients suffering from Huntington's chorea are at higher risk of intraoperative complications, including pulmonary aspiration,[1] a prolonged response to succinylcholine[3] and thiopental,[5] and increased sensitivity to midazolam.[6] The primary goal in general anaesthesia for these patients is to provide airway protection and a rapid and safe recovery. The development of new short-acting drugs, such as propofol, has led to recommendation of a total intravenous anaesthesia (TIVA) technique[6–8] in patients with Huntington's chorea, thus avoiding compromised postoperative recovery and the increased risk of postoperative shivering from potent inhalational agents. However, the recently introduced inhalational agent sevoflurane could eliminate the problem of prolonged recovery because of its favourable pharmacokinetic profile. Secondly, the use of the short-acting, non-depolarizing neuromuscular blocking drug mivacurium could provide adequate relaxation without

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the danger of prolonged paralysis at the end of the operation.

Case report

A 17-yr-old, 85 kg girl with a 4-yr history of Huntington's chorea was admitted for urgent appendectomy. Her sister had died from Huntington's chorea at the age of 25 yr. She suffered from progressive dementia and swallowing dysfunction with regurgitation, but was not taking any medication. She appeared anxious and uncooperative and did not respond appropriately to verbal commands. Laboratory investigations were normal.

To minimize the risk of aspiration, we performed rapid-sequence induction consisting of thiopental 400 mg and succinylcholine 100 mg with cricoid pressure applied. To determine the degree of muscle relaxation we used train-of-four (TOF) monitoring (Innervator; Fisher & Paykel Health Care, Auckland, New Zealand). After induction the TOF was no longer detectable and the trachea was intubated. Within 10 min, all four twitches of the TOF returned to control levels and mivacurium 10 mg was administered. Anaesthesia was maintained with fentanyl 0.25 mg and sevoflurane 1.5–2% inspired. After 15 min, a second increment of mivacurium 10 mg was given, as four twitches were detectable and the TOF ratio was >0.75. At the end of surgery, which lasted 70 min, the TOF had recovered to control values and sevoflurane was discontinued. After 5 min the patient regained consciousness and was extubated uneventfully without any reversal of residual neuromuscular block. To prevent postoperative nausea and vomiting, and thus reduce the risk of aspiration, we administered ondansetron 8 mg and ranitidine 50 mg i.v. The postoperative course was uneventful except for a short episode of shivering, which was successfully treated with pethidine 50 mg. The patient was discharged from hospital on the third postoperative day.

Discussion

Different anaesthetic techniques have been recommended for use in patients suffering from Huntington's chorea. Spinal anaesthesia has successfully been performed in one patient.[9] Some authors recommend using a TIVA technique and avoiding potent inhalational agents to reduce the risk of postoperative shivering and the precipitation of generalized tonic spasms.[6–8] Others have used inhalational agents, such as halothane[2] and isoflurane,[4] without problems. In spite of recommendations to avoid potent inhalational agents,[6–8] we decided to use sevoflurane to maintain anaesthesia because of its favourable pharmacological properties. It is easy to titrate and provides rapid recovery. It proved to be effective and safe in our patient; the short episode of postoperative shivering did not evoke generalized spasms and was easily treated by the administration of pethidine.

We did not find any prolonged effects from thiopental or succinylcholine, which have been found previously.[3 5] The cause of the prolonged response to succinylcholine, as found in one patient in a previous report,[3] may have been abnormal plasma cholinesterase and completely unrelated to Huntington's chorea.[4] The use of rocuronium for rapid-sequence induction in this patient might have been a feasible alternative, but the authors' experience concerning rocuronium was too limited at that time. The recovery time for mivacurium was within the range reported in normal patients who have received similar doses. We could not find any evidence of altered mivacurium pharmacodynamics in our patient despite prior administration of succinylcholine.

The use of sevoflurane and mivacurium for general anaesthesia in patients suffering from Huntington's chorea seems to be effective and safe.

References

1 Stoelting RK, Dierdorf SF, McCammon RL. *Anesthesia and Co-existing Disease*. New York: Churchill Livingstone, 1988; 307

2 Farina J, Rauscher LA. *Anaesthesia* and Huntington's chorea. A report of two cases. *Br J Anaesth* 1977; **49**: 1167–8

3 Gualandi W, Bonfanti G. A case of prolonged apnoea in Huntington's chorea. *Acta Anaesthesiol (Padova)* 1968; **19**: 235–8

4 Costarino A, Gross JB. Patients with Huntington's chorea may respond normally to succinylcholine. *Anesthesiology* 1985; **63**: 570

5 Davies DD. Abnormal response to anaesthesia in a case of Huntington's chorea. *Br J Anaesth* 1966; **38**: 490–1

6 Rodrigo MRC. Huntington's chorea: midazolam, a suitable induction agent? *Br J Anaesth* 1987; **59**: 388–9

7 Kaufman MA, Erb T. Propofol for patients with Huntington's chorea? *Anaesthesia* 1990; **45**: 889–90

8 Johnson MK, Heggie NM. Huntington's chorea. A role for the newer anaesthetic agents. *Br J Anaesth* 1985; **57**: 235–6

9 Fernandez IG, Sanchez MP, Ugalde AJ, Hernandez CM. Spinal anaesthesia in a patient with Huntington's chorea. *Anaesthesia* 1997; **52**: 391

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BJA

COMMENTARY

Experience of a major incident alert at two hospitals: 'The Soho Bomb'

K. N. Williams* and S. Squires

Guy's and St Thomas' Hospitals, London, UK and McIndoe Burns Centre, Queen Victoria Hospital, East Grinstead, UK

**Corresponding author: Anaesthetic Department, 1st Floor, East Wing, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK*

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At 18:37 h on Friday 30 April 1999, a nail bomb exploded without warning in the Admiral Duncan public house in Soho, London; two victims died at the scene. At 19:05 h the London Ambulance Service issued Major Incident Alerts or Standbys at six London Hospitals, including Guy's Hospital and St Thomas' Hospital (STH).

The Guy's and St Thomas' experience

The first ambulance arrived at STH at 19:15 h and the last of 36 patients arrived at 21:00 h. The telephone switchboard contacted anaesthetists from 19:21 h onwards. Guy's Hospital received 23 patients, none of whom required admission. At STH, 27 patients with minor injuries were treated and discharged from the Accident and Emergency (A&E) department, four patients were admitted directly to the operating theatre, four were admitted to the wards and one was transferred from the A&E department to the Burns Unit of the Queen Victoria Hospital, East Grinstead. Physical injuries included burns, macerated and fractured limbs, an acute abdomen and multiple shrapnel wounds. All patients were presumed to be an infection risk and suitable precautions were taken.

A total of 70 medical staff attended A&E and the operating theatres; 36 were consultants, of whom 12 were anaesthetists; countless other staff appeared, mainly on their own initiative. Surgery at STH started at 21:00 h (day 0) and ended at 03:30 h the following morning; four operating tables worked throughout this period (sufficient staff were available to have opened two more operating theatres if needed).

Operative procedures on day 0 included: extensive debridement of soft tissue wounds; a colostomy for blast injury to the sigmoid colon; two completion below-knee amputations; one above-knee amputation; external fixation of a right and a left ulnar fracture (on different patients); and a completion amputation of the left middle finger. One patient narrowly avoided a thoracotomy when a nail, clearly visible on chest x-ray, was removed from subcutaneous tissues by an alert thoracic surgeon.

Two patients (patients 1 and 4 in Table 1) were transferred after their operation to the 15-bed Intensive Therapy Unit (ITU; which also admitted two cardiac arrests from medical wards during this period), and two patients (patients 3 and 5) were ventilated in our nine-bed Overnight Intensive Recovery facility (OIR; normally used by patients after cardiac surgery).

On day 1, three patients were re-anaesthetized: patient 4 for a CT scan of the cervical spine, patient 5 for suture of a previously identified penetrating eye injury, and patient 1 for further debridement, removal of nails and grafting of wounds. Extensive cavitation wounds beneath trivial skin punctures were particularly evident. Patient 3 had extensive burns and a tibial fracture treated by external fixation on day 0; on intubation the anaesthetist observed laryngeal oedema, and therefore on day 1 a bronchoscopy was performed; this showed no evidence of smoke inhalation. The patient was extubated and, after 16 h of uneventful spontaneous ventilation on air, he was transferred on day 2 to East Grinstead (see below).

By the end of the 4-day Bank Holiday weekend, 36.5 h of operating had been performed on five patients during 12 procedures. A total of 71 units of blood, 40 units of FFP and

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Table 1 Course of events for five patients up to day 63. AKA = above-knee amputation; BKA = below-knee amputation; L, left, R, right

Patient	Main injuries	Number of days on				Number of operations
		OIR	ITU	HDU	Ward	
1	25% burns, L ulnar fracture, L AKA	1	26	7	29	8
2	R arm fracture, burns	0	0	0	17	2
3	30% burns, R tibial fracture (+4 operations at East Grinstead)	2	0	0	0	1
4	Perforated colon, bilateral BKA, ?C5/6 lesion	0	17	8	38	8
5	R radial fracture, shrapnel R leg and arm, R global perforation of eye	10	7	8	38	7
Total		13	50	23	122	26

thirteen 250-ml bags of platelets were transfused over this period; blood and blood products were provided without delay. On Day 4, three of the patients in Table 1 returned to the operating theatre together with one of the ward patients. Patient 5 remained in the OIR for 10 days before returning to a High Dependency Unit (HDU); he was shortly thereafter admitted to the ITU with *Klebsiella* pneumonia. He and patient 1 subsequently developed severe respiratory and cardiovascular problems requiring a variety of interventions, including inotropes, prone ventilation, inhaled nitric oxide and percutaneous tracheostomy; neither patient required haemofiltration. None of our patients sustained head injuries. The clinical course of the patients operated upon at STH is summarized in Table 1; all survived.

These five patients required continuing care. Patient 3 underwent a below-knee amputation on day 188 (7 months later); on that day, four of the five patients listed in Table 1 were still in-patients at STH, although none had been resident continuously since day 0.

The East Grinstead experience

The patient who was transferred from STH on day 2 (patient 3) required operative intervention; three other patients were admitted to East Grinstead Hospital after the incident from other units. On arrival, the STH patient had a 33% flash burn mainly affecting the trunk, arms and face, together with a right tibial fracture in external fixation and shrapnel wounds to the lower limbs and left shoulder; nevertheless, his overall condition was satisfactory. The following day he deteriorated with generalized sepsis and hypoxia. Morphine-resistant pain in his right foot prompted a fasciotomy on day 3 and, although per-operative bronchoscopy again failed to show evidence of smoke inhalation, he was electively ventilated and extubated on day 4. On day 7, the upper tibial wound was closed with a local fasciocutaneous flap and the fasciotomies and shoulder wound were repaired with split skin grafts. He underwent three further operative procedures before he returned to STH on day 24.

The lessons to be learned

Overall, the Major Incident Procedure at STH worked well, but improvements could be made.

Communication

A well-attended debriefing held on day 6 revealed a number of communication failures and exposed our failure to plan adequately for the *subsequent* load on the operating theatres, which continued for many days after the incident.

- Bleeps were a hopeless means of contact since the switchboard (which received 1500 calls in 1 h) could not possibly keep track of who had or had not answered.
- Our automated call-routing system enables callers with touch-tone telephones to dial the extension they require themselves and handles up to 12 calls simultaneously; this proved adequate.
- The anaesthetic staff list held by the switchboard was 18 months out of date, and new consultants were thus left undisturbed whilst those long-since retired were invited to attend.
- Several anaesthetists asked to be put through to A&E to confirm the Incident Alert, which blocked external and internal lines, probably without a successful connection; we have since arranged for a direct line to the operating theatres for anaesthetists.
- Those in A&E had difficulty contacting the operating theatres, and *vice versa*, and a more direct link between the surgeon in A&E and the anaesthetist in the operating theatres has now been established.
- A&E staff commented that, in the mêlée, anaesthetists were difficult to identify and clearer marking was requested (purple baseball caps?).

Staffing

- The four resident anaesthetic trainees, the on-call general and the on-call cardiac consultant coped adequately with the operating theatre load on day 0 with the help of one extra consultant volunteer. Calling in as many as ten further consultants was probably unnecessary, though their efforts were greatly appreciated in A&E and for inter-hospital transfers. However, additional help was needed after day 0 to cover anaesthetic services over a long weekend.

- At 11:00 h on day 1, the resident staff and the on-call general anaesthetic consultant were all anaesthetizing patients simultaneously when a patient with 'acute epiglottitis' was admitted to A&E. Coincidentally, the same consultant who volunteered to help in the operating theatre on day 0 arrived, and he was instantly despatched to sort out what transpired to be a quinsy that responded, at least initially, to medical treatment. We needed reminding that resources to deal with 'ordinary' emergencies are still needed, regardless of Major Incident Alerts.

Facilities

- ITUs are often at their busiest on a Friday so, if the word can be used in such a context, it is fortunate that this event occurred on this particular Friday of a Spring Bank Holiday weekend when beds happened to be available and three consultant ITU staff were still in the hospital. Simultaneous provision of intensive care for five extra critically ill patients might have been impossible at other times, particularly in the winter, when bed occupancy is supramaximal.
- The clinical courses of the patients at STH and East Grinstead were punctuated with episodes of systemic sepsis, possibly secondary to infected shrapnel fragments, which required intense supportive measures. All patients were young and previously healthy, and eventually made a reasonable physical recovery.

  Peripheral specialist units such as the Queen Victoria Hospital at East Grinstead can only accept patients with conditions appropriate to their facilities. This requires careful consideration before patients from major incidents who might require intensive care are referred.
- Long-term psychological and social support is deemed essential for both victims and carers.[1] Counselling was offered to all involved, though uptake was patchy amongst the staff. The five patients listed (Table 1) required extensive psychological and social support and 16 of the 'walking wounded' were counselled.

Conclusions

We found that, in such an obvious emergency, staff availability was not a problem. Communication within and without the receiving hospital can be improved; bleeps, both internal and air-call, are unreliable, and direct telephone lines should be established. Anaesthetic and other resources must be provided for several days after such an incident. Patients with potential multi-organ failure should not be referred to specialist units without due consideration and consultation.

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So extensive was the help we received at the time of the incident and in the preparation of this manuscript that we cannot possibly acknowledge it individually, but nonetheless we wish to express our thanks.

Reference

1 Adshead G. Treatment of victims of Trauma. In: Lee A, ed. *Affective and Non-psychotic Disorders: Recent Topics from Advances in Psychiatric Treatment*, Vol. 2. London: Gaskell, 1999; 145–55

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Correspondence

Patients yes; politics no

Editor—Hopkins[1] writes that it is wrong, just because of the political packaging, to dismiss the fundamental ideas behind developments such as clinical governance and the National Institute for Clinical Excellence (NICE). But the fundamental ideas *are* political. They are intended to enable managerial control of health professionals by using the methods of accountancy.[2] Eventually, whether a clinician is good or bad will be judged not on outcomes (which is what Hopkins is, rightly, keen to pursue) but on whether they have followed the processes to ensure quality. This is despite the lack of evidence that the processes ensure quality in the first place. We were told at their inception that clinical governance and NICE would improve quality, but there has been little intellectual debate. Instead, critics of these developments are dismissed as not wanting quality. In fact, if one examines the way NICE is supposed to work and the principles on which it is based, there are serious difficulties that suggest it cannot work in the way it is intended, or in which most clinicians would hope.[3]

Hopkins wants us to seize the opportunity to develop quality assurance based on meaningful outcomes; others have spoken of how clinical governance will prove the need for more funding for the National Health Service in the UK. All are deluded. In the present climate, our efforts will be taken by the managers to ensure that clinicians become no more than functionaries, carrying out medical procedures according to algorithms from which we deviate at our peril. For years, clinicians have complained of NHS underfunding. Ignoring this is a real problem, and exaggerating the extent of poor professional performance, clinical governance was yet another distracting reorganization, which itself was underfunded.

Whatever outcomes we look for in anaesthesia, we have to accept that they will be soft ones. We do indeed need to research what is best for our patients. We also need to remember that the large randomized trials that Hopkins asks for, while being the only way of obtaining this information, will never in themselves tell us what to do for an individual patient.

N. W Goodman
Department of Anaesthesia
Southmead Hospital
North Bristol NHS Trust
Bristol

1 Hopkins PM. Editorial I. A shame about the patient? *Br J Anaesth* 2000; **84**: 1–2
2 Charlton BG. The ideology of 'accountability'. *J R Coll Phys Lond* 1999; **33**: 33–5
3 Miles A, Hampton J, Hurwitz B, eds. *NICE, CHI and the NHS reforms: enabling excellence or imposing control?* London: Aesculapius Medical Press, 2000

Editor—I would like to thank Dr Goodman for his interest in my editorial:[1] I enjoyed reading his letter. I am pleased that Dr Goodman agrees that we should pursue meaningful outcomes as indicators of quality. It would be idyllic if we could do this in a political vacuum. But we cannot: while the maintenance of political power is heavily dependent on the electorate's perception of the government's management of the National Health Service (NHS), provision of health care in the UK will remain a political issue. Does Dr Goodman believe that we are not already subject to 'managerial control of health professionals by (using) the methods of accountancy'? What I have found objectionable is that the only criterion used previously for this managerial control was short-term cost. There was no regard given to the quality and value of what was provided. These were the fundamental ideas I referred to in my editorial.[1]

Dr Goodman is concerned that quality assurance processes will be used to judge clinicians and hospitals. To share this concern, one only has to have experienced the Higher Education Quality Assurance Agency's subject review process, in which university departments have had their teaching graded on the basis of the 'quality process' rather than the quality of the teaching. This must not happen with health provision and is precisely why we must determine relevant measures of quality in the ways suggested in my editorial.[1]

I may, as Dr Goodman believes, be deluded in thinking that we can use the current political initiatives to achieve the best for our patients. I contend that failing to try will result inevitably in a poorer health service.

P M Hopkins
Academic Unit of Anaesthesia
St James's University Hospital
Leeds

1 Hopkins PM. Editorial I A shame about the patient? *Br J Anaesth* 2000, **84**: 1–2

Anaphylactic reactions to rocuronium

Editor—We were interested in the article by Neal and colleagues,[1] and would like to make some comments.

The authors reported three cases of anaphylactoid reactions to rocuronium, for which they discussed an immune mechanism without confirming it, because they only used prick tests with 1:10 dilution. Positive prick tests with rocuronium, a poor histamine releaser,[2] in 1:10 dilution, are highly suggestive of IgE dependent anaphylaxis, especially in case 1 where the test was already positive with 1:100 dilution and where an elevated concentration of tryptase, which is a valuable indicator of anaphylaxis,[3] had been detected.

From our long experience with hundreds of patients tested with all the neuromuscular blocking agents, using prick tests and intradermal tests (IDT), we maintain that in normal patients, who are not allergic to muscle relaxants, the aminosteroidal neuromuscular blocking agents never induce a positive response to prick tests in 1:10 dilution, or with undiluted solution, in contrast to atracurium and mivacurium. We are therefore certain that the three cases reported by Dr Neal are due to true IgE dependent anaphylaxis to rocuronium.

The authors doubt the validity of their cutaneous tests in diagnosing anaphylaxis, referring to the work of Levy conducted in control subjects (personal communication), where 90% were positive to rocuronium tested in 1:10 dilution. But the cutaneous tests used by Levy were IDTs and not prick tests, and it is well known that these two types of skin tests are not comparable with respect to the amount of drug injected into the skin.

The prick tests are epidermal tests. The skin is pricked with the

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tip of an intradermal needle or a special device applied through a drop of the drug to be tested. The volume of the tested solution introduced into the epidermis has been evaluated as 20 nanol, but only 5 nanol reach living cells in the epidermis.[4] With IDT, a volume of 0.03 ml to 0.05 ml of the solution is injected into the dermis, which is 30 000–50 000 nanol. The difference is of a factor from 1–10 000. For this reason, when prick tests are negative, it is advisable to begin IDT with a solution diluted to 1:1000 to test the equivalent dose to that used in the prick test. In fact, this point was underlined in section 6 of the guidelines published in 1995 by the working party of the Association of Anaesthetists of Great Britain and Ireland and the British Society of Allergy and Clinical Immunology.[5] Control subjects studied by Levy had therefore received into the dermis a quantity of rocuronium 1000 times greater than the quantity injected into Dr Neal's patients.

It is a pity that the detection of specific IgE against quaternary ammonium ions, and an inhibition test to rocuronium, were not performed on the three patients. For some time, the two techniques of detection have been available and used as a routine in France.[6 7] These techniques both have an 85% sensitivity rate,[8] in contrast to the Pharmacia RAST succinylcholine test in which sensitivity is between 45 and 70%.[6 8] If specific antibodies to rocuronium had been detected, this would have enabled Dr Neal and colleagues to confirm the immunological nature of the reaction.

The authors state that they are aware of only one other published case.[9] We should like to note the results of the fourth epidemiological survey concerning anaphylactoid reactions occurring during anaesthesia in France between 1994 and 1996, published in *Annales Françaises d'Anesthésie et de Réanimation* in 1999.[10] Out of 452 cases of anaphylaxis due to neuromuscular blocking drugs, 41 were induced by rocuronium. In the October 1999 issue of the same journal, four serious case of rocuronium anaphylaxis occurring in 1998 were also published.[11]

Dr Neal and his colleagues conclude by suggesting the need for close monitoring of the frequency of reactions to rocuronium. We agree, but there is no reason to focus solely on this muscle relaxant. This policy of monitoring anaphylactic reactions to anaesthetic agents has been applied throughout France since 1985.[12–14] The fifth survey concerning cases of anaphylaxis observed during anaesthesia in 1997 and 1998 will be published shortly.

M C. Laxenaire
Department of Anaesthesia and Intensive Care

D. A. Moneret-Vautrin
Department of Medicine and Clinical Immunology and Allergology
CHU Hôpital Central, Nancy, France

1 Neal S McD, Manthri PR, Gadiyar V, Wildsmith JAW. Histaminoid reactions associated with rocuronium. *Br J Anaesth* 2000; **84**: 108–11
2 Naguib M, Samarkandi AH, Bakhamees HS, Magboul MA, le-Bakry AK Histamine release and haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine *Br J Anaesth* 1995; **74**: 588–92
3 Fisher MM, Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. *Br J Anaesth* 1998; **80**: 26–9
4 Moneret-Vautrin DA, Laxenaire MC. Skin tests in diagnosis of allergy to muscle relaxants and other anaesthetic drugs. Allergic Reactions to Anaesthetics. Clinical and Basic Aspects *Monogr Allergy* 1992; **30**· ESK Assem, Basel: Karger. 145–55
5 The Association of Anaesthetists of Great Britain and Ireland and the British Society of Allergy and Clinical Immunology. Suspected Anaphylactic Reactions Associated with Anaesthesia. Revised Edition 1995
6 Guéant JL, Mata E, Monin B, Moneret-Vautrin DA, Kamel L, Nicolas JP, Laxenaire MC. Evaluation of a new reactive solid-phase for radioimmunoassay of seric specific IgE against muscle relaxant drugs. *Allergy* 1991; **46**: 452–8
7 Guilloux L, Ricard-Blum S, Ville G, Motin J. A new radioimmunoassay using a commercially available solid support for the detection of IgE antibodies against muscle relaxants. *J Allergy Clin Immunol* 1992; **90**: 153–9
8 Guilloux L, Ricard-Blum S, Ville G, Motin J. Histamine release assay and radioimmunoassay for the detection of IgE antibodies against neuromuscular blocking drugs. *Ann Fr Anesth Réanim* 1993; **12**: 182–6
9 Yee R, Fernandez JA. Anaphylactic reaction to rocuronium bromide *Anaesth Intensive Care* 1996; **24**: 601–4
10 Laxenaire MC et le Groupe d'études des réactions anaphylactoides peranesthésiques. Epidémiologie des réactions anaphylactoides peranesthésiques. Quatrième enquête multicentrique (juillet 1994–décembre 1996). *Ann Fr Anesth Réanim* 1999; **18**: 796–809
11 Barthelet Y, Ryckwaert Y, Plasse C, Bonnet-Boyer MC, d'Athis F. Accidents anaphylactiques graves après administration de rocuronium. *Ann Fr Anesth Réanim* 1999; **18**. 896–900
12 Laxenaire MC, Moneret-Vautrin DA, Widmer S, Mouton C, Guéant JL. Substances anesthésiques responsables de chocs anaphylactiques. Enquête multicentrique française. *Ann Fr Anesth Réanim* 1990; **9**. 501–6
13 Laxenaire MC and the Members of the Writing Committee. Drugs and other agents involved in anaphylactic shock occurring during anaesthesia. A French multicentre epidemiological inquiry. *Ann Fr Anesth Réanim* 1993; **12**: 91–6
14 Laxenaire MC et le Groupe d'études des réactions anaphylactoides peranesthésiques Substances responsables des choçs anaphylactiques peranesthésiques. Troisième enquête multicentrique française (1992–1994). *Ann Fr Anesth Réanim* 1996; **15**: 1211–8

Post-dural puncture headache associated with cerebral venous thrombosis

Editor—The article by Stocks and colleagues made for interesting reading.[1] Peripartum post-dural puncture headache (PDPH) associated with cerebral venous thrombosis (CVT) is a diagnostic and therapeutic challenge.

While peripartum CVT is rare in developed countries, rates in developing countries are much higher, account for a vast database. Incidences of peripartum CVT as high as 200–500 per 100 000 deliveries have been reported in India, accounting for 60% of all cases.[2] Mortality from puerperal CVT may reach 28–33%.[3] A recent retrospective study of 60 patients, aged 18–46 yr, with peripartum ischaemic cerebrovascular accidents found CVT to be almost as frequent (55% *vs* 45%) and with a higher mortality (36% *vs* 0%) than cerebral ischaemic accidents (CIA).[4] Computerized tomography (CT) scan findings in 25 peripartum CVT patients have been described as diffuse brain oedema (52%), haemorrhagic or nonhaemorrhagic infarctions on one or both sides of the brain (48%), gyral enhancement (40%) and tentorial enhancement (16%).[5] Common modes of presentation include headache (92%), altered sensorium (80%), seizures (76%), papilloedema (80%) and hemiplegia (52%).

Cantu and co-workers studied the characteristics of 67 patients with CVT associated with pregnancy and the puerperium, and compared them with those of 46 patients with non-obstetric related CVT.[6] They found that patients with peripartum CVT were younger (average age 27 yr *vs* 36 yr), had a more acute onset of symptoms (82% *vs* 54%; $P=0.003$), had a quicker plateau of symptoms (70% *vs* 45% in 10 days; $P=0.01$), had a good prognosis (80% *vs* 58%; $P=0.01$) and had lower mortality rates (9% *vs* 33%; $P=0.002$). They concluded that CVT associated with pregnancy and the puerperium has a better prognosis than that due to other causes.

When a patient has minimal relief from two extradural blood patch (EBP) therapies for PDPH, we recommend the use of fluoroscopic guided EBP therapy, with epidural needle placement determined by means of a limited epidurogram. A clinical, prospective double-blinded trial over a period of 6 months involving 19 patients at our pain-management clinic compared favourably for fluoroscopic-guided as compared to blind EBP treatments for PDPH.[7] Repeat EBP therapies were avoided and better pain control, as measured by visual analogue scales, was achieved. Correct epidural needle placement and avoidance of repeat inadvertent dural punctures are some of the features that affected better outcomes.

This information, in conjunction with that offered by the authors, helps us understand more clearly the characteristics of peripartum CVT. Since many of these patients would receive epidural analgesia in labour, differentiation of headache caused by CVT from PDPH would be critical in terms of management and prognosis.

A Anand
The Pain Clinic
Milwaukee
WI, USA

1 Stocks GM, Wooler DJA, Young JM, Fernando R. Postpartum headache after epidural blood patch: investigation and diagnosis. *Br J Anaesth* 2000; **84**: 407–10

2 Lamy C, Sharshar T, Mas JL. Cerebrovascular diseases in pregnancy and puerperium. *Rev Neurol* 1996; **152**: 422–40

3 Srinivasan K. Cerebral venous and arterial thrombosis in pregnancy and puerperium A study of 135 patients. *Angiology* 1983; **34**: 731–46

4 Ben Hamouda-M'Rad I, Mrabet A, Ben Hamida M. Cerebral venous thrombosis and arterial infarction in pregnancy and puerperium. A series of 60 cases. *Rev Neurol* 1995; **151**: 563–8

5 Sanchetee PC, Dhamija RM, Roy AK, Venkatraman S. Peripartum cerebral venous thrombosis *J Phys India* 1992; **40**: 664–6

6 Cantu C, Barinagarrementeria F. Cerebral venous thrombosis associated with pregnancy and puerperium. Review of 67 cases. *Stroke* 1993; **24**: 1880–4

7 Anand A, Ellias M. Blind versus fluoroscopic technique of epidural blood patch for treatment of post-dural puncture headache. *Proceedings of the Midwest Anesthesia Residents' Conference*, 2000; A

Editor—Thank you for the opportunity to respond to Anand's letter. We welcome his interest in our case report and the additional information regarding peripartum cerebral vein thrombosis.

With regard to the use of the fluoroscopic guided epidural blood patch therapy, this is of interest, and to our knowledge has not been described in the obstetric population. Epidural fluoroscopy has been used to aid placement of epidural steroid injections in patients with chronic back pain[1] and has been shown to be safe and accurate.[2] However, we would not support the recommendation that fluoroscopic guided epidural blood patch therapy should be used in patients who have had minimal pain relief with two epidural blood patches. As discussed in our case report, it is in precisely this clinical situation that doubt exists regarding the aetiology of persistent postpartum headache. Other more serious pathologies must be considered as well as the possibility that the epidural space was not located properly in previous epidural blood patch attempts. Often clinicians cannot be certain of the diagnosis without further investigation and until other pathologies are excluded, we feel that a further epidural blood patch should not be attempted. If, after this, it is concluded that a further epidural blood patch may be of benefit, then in these circumstances epidural fluoroscopy may be of help in successful location of the epidural space.

G. M. Stocks
D. J. A. Wooler
J. M Young
R. Fernando
London

1 Renfrew DL, Moore TE, Kathol MH, el-Khoury GY, Lemke JH, Walker CW. Correct placement of epidural steroid injections: fluoroscopic guidance and contrast administration. *Am J Neuroradiol* 1991; **12**: 1003–7

2 Johnson BA, Schellhas KP, Poller SR. Epidurography and therapeutic epidural injections: technical considerations and experience with 5334 cases. *Am J Neuroradiol* 1999, **20**: 697–705

Magnesium sulphate for pre-eclampsia and a sudden bradycardia

Editor—The value of magnesium sulphate ($MgSO_4$) in the treatment of eclampsia is established[1] but it is unclear whether it has any prophylactic anticonvulsant value. An important randomized placebo controlled trial (MAGPIE) is studying the use of magnesium in pre-eclamptic patients and will report on the influence of magnesium on eclampsia and its complications.[2] Currently there is little information on the toxicity and side-effects of magnesium in obstetric practice and the MAGPIE trial will provide important data on this issue. The incidence and significance of side-effects may only be revealed as use of the drug increases I would like to report a significant bradycardic event that occurred in a pre-eclamptic patient who was receiving $MgSO_4$.

An 18-yr-old, previously fit primagravidae patient was admitted to the delivery suite at 36 weeks gestation with proteinuria and hypertension. Her mean arterial pressure (MAP) was 145 mm Hg and required urgent treatment. She was on no medication. After assessment, she received a bolus of intravenous hydralazine 10 mg which lowered the MAP but caused the pulse rate to increase from 100 to 150–160 beat min^{-1}. The patient experienced palpitations and was connected to an electrocardiograph (ECG) monitor which revealed a sinus tachycardia. To treat the tachycardia and further lower the MAP, intravenous labetolol 30 mg was given in 10 mg boluses over the next 30 min. This reduced the MAP to 120 mm Hg and pulse rate to 110–120 beat min^{-1}. As the cardiovascular parameters had improved, no further antihypertensive agents were given.

The patient's condition satisfied the entry criteria into the MAGPIE trial and an infusion was prepared from the MAGPIE drug pack. The trial is blinded but I subsequently ascertained that the trial drug was $MgSO_4$. The loading dose of magnesium 4 g is infused over 10–15 min although in our unit we give the loading dose over 30 min. Approximately 20 min after the infusion was started, the patient suddenly complained of feeling faint, looked pale and started to lose consciousness. The ECG monitor showed that the heart rate had dropped from 110 to <40 beat min^{-1} with several periods where there was no electrical activity. The infrequent complexes on the single ECG monitor trace had normal morphology. Her arterial pressure remained at 125/75 mm Hg. At the time of the sudden bradycardia, the patient was comfortable and relaxed and had no obvious precipitating event to cause a vasovagal attack. She was sitting fully upright and aortocaval compression therefore seemed unlikely. She had not received any labetolol for at least 30 min and her pulse rate had remained consistently over 100 beat min^{-1} prior to commencing the trial infusion.

The patient was put in the left lateral position and given 15 litres min^{-1} high flow oxygen through a Hudson face mask.

The magnesium infusion was stopped and intravenous atropine 200 mcg was given. The patient did not lose consciousness but continued to feel faint over the following 5 min until the pulse rate increased to 70 beat min^{-1}. The magnesium infusion was recommenced approximately 10 min after the bradycardia and when the loading was complete a maintenance infusion of $MgSO_4$ 1 g h^{-1} was started. No further episodes of bradycardia occurred. The patient remained stable with a MAP <120 mm Hg and a pulse rate of 80–100 beat min^{-1}. Ninety minutes later, despite stabilization of the hypertension, it was decided to deliver the baby. A healthy baby was delivered by Caesarean section under spinal anaesthesia and the postoperative care of the mother and baby was uneventful.

The side effects of magnesium have been reviewed by Fawcett and colleagues[3] and it is known that magnesium can cause a bradycardia by decreasing sinus node rate, prolonging AV conduction time and increasing AV node refractoriness.[4] I did not measure the plasma magnesium level at the time of the bradycardia but it should not have been in the cardiotoxic range. However, I suspect that the plasma concentration of magnesium necessary to produce cardiac side-effects when combined with a beta blocker may be lower than quoted. As magnesium is a physiological calcium antagonist,[5] similar drug interactions are well documented. When pharmacological calcium antagonists such as verapamil and nifedipine are combined with beta adrenoreceptor antagonists, the potential risk of bradycardia and asystole is well known and their co-administration is to be avoided.

Having identified a theoretical explanation for the bradycardia, I was surprised to find no previous reports of this drug interaction or any reference to the combined effect of magnesium and beta adrenoreceptor antagonists on myocardial function. As both drugs have been given in combination to many patients, this case appears to represent a rare side-effect. However, it is possible that it occurs more frequently but in a less severe form which clinicians have not detected or reported. In our unit, patients that are receiving $MgSO_4$ now have ECG monitoring. I note that this is not required in the MAGPIE protocol.

J. A. L. Pittman
Department of Anaesthesia
Gloucester Royal Hospital
Gloucester

1 Roberts JM. Magnesium for pre-eclampsia. *N Eng J Med* 1995; **333**: 250–51
2 Magnesium sulphate for treatment of pre-eclampsia: a trial to evaluate the effects on women and their babies. Protocol. Magpie trial co-ordinating centre, Oxford, 1998
3 Fawcett WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. *Br J Anaesth* 1999; **83**: 302–20
4 Dicarlo L, Morady F, Buitleir M, Krol R, Schurig L, Annesley T. Effects of magnesium sulphate on cardiac conduction and refractoriness in humans. *J Am Cardiol* 1986; **7**: 1356–62
5 Iseri LT, French JH. Magnesium. nature's physiological calcium blocker. *Am Heart J* 1984; **108**: 188–94

Dexamethasone reduces nausea and vomiting after laparoscopy

Editor—Wang and colleagues have stated in two recent studies[1 2] that 'extensive literature searching' failed to identify a single report of side-effects attributable to one dose of dexamethasone.

As part of our research, we performed a literature search on PubMed and identified single dose intravenous administration of dexamethasone implicated in the aetiology of perineal irritation.[3 4] We also have experience that administration of intravenous dexamethasone to conscious patients can cause unpleasant burning sensations in the perineal area. The summary of product characteristics for dexamethasone injection draws attention to 'a transient burning or tingling sensation mainly in the perineal area following intravenous injection of large doses of corticosteroid phosphates'. As a consequence of these findings, our protocol for administration of intravenous dexamethasone is after induction of general anaesthesia.

In the first of the two studies, Wang specifies that dexamethasone was administered 1 min before induction of anaesthesia, and in the second 'at the time of induction'. Our experience is that patients who get such perineal irritation have complained immediately. Such patients are likely to identify themselves as dexamethasone recipients. We therefore call into question whether either or both of these studies were truly double-blinded. Additionally, we have concerns about the ethics of placebo controls in patient groups identified as 'high risk' for postoperative nausea and vomiting.

R. Thomas
N. Jones
Department of Anaesthetics
North Hampshire Hospital
Basingstoke

1 Wang JJ, Ho ST, Liu YH, *et al.* Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. *Br J Anaesth* 1999; **83**: 772–5
2 Wang JJ, Ho ST, Liu YH, *et al* Prophylactic antiemetic effect of dexamethasone in women undergoing ambulatory laparoscopic surgery. *Br J Anaesth* 2000; **84**: 459–62
3 Baharav E, Harpaz D, Mittleman M, Lewinski UH Dexamethasone-induced perineal irritation. *N Engl J Med* 1986, **314**: 515–6
4 Sartiano GP, Rosenblum SL, Brady ME. More on dexamethasone-induced perineal irritation *N Engl J Med* 1986; **314**: 1643–4

Editor—Thank you for the opportunity to respond to the letter from Thomas and Jones. In answer to the three questions:

First, we would like to thank Thomas and Jones for the valuable comments about the dexamethasone-related perineal irritation. There have been three letters concerning this side-effect, according to a Medline literature search on the last 20 yr. In previous searching, we only focused on other side-effects of dexamethasone, such as peptic ulcer, infection, electrolyte imbalance, hypertension, delayed wound healing, immune suppression, etc, and missed these reports. Your comment is greatly appreciated.

Second, since 1981, dexamethasone has been extensively used in the prophylaxis of nausea and vomiting in patients undergoing chemotherapy and following surgery.[1–8] But no well-designed study reported perineal irritation after dexamethasone in conscious patients. The incidence of dexamethasone-related perineal irritation must be low. Furthermore, we have experience of the use of dexamethasone in more than 500 conscious patients to treat bronchial asthma, urticarial transfusion reactions, acute laryngeal oedema and drug reactions, and to prevent PONV. For these purposes, dexamethasone was given intravenously under the supervision of anaesthetists either in the operating room or in the post-anaesthetic care unit. No patient reported such a side-effect. This method of drug administration was also accepted in previous studies.[1–4] Our studies were conducted under a double-blind design.

Our studies were also conducted after obtaining institutional review board approval and written informed consent from patients.

For routine patient care, our patients stay for 2 h in the postanaesthetic care unit if they are out-patients and 1 h if they are in-patients. But in these studies, all patients stayed for 4 h in the postanaesthetic care unit. No antiemetic is given prophylactically in our clinical practice; they all were given as rescue antiemetics. In our studies, all patients received the same antiemetic management as other patients. From our studies, we found that PONV occurred more frequently within 0–4 h postoperatively (more than 75% of PONV first occurred in this period) than from 4–24 h postoperatively. This study design of using a placebo control has been adopted in many of the clinical studies evaluating PONV in high risk groups,[5] although we agree that it is probably no longer considered ethically acceptable.

J. J. Wang
S. T. Ho
H. S. Liu
C. M. Ho
Department of Anesthesiology and Obstetrics and Gynecology
Tri-Service General Hospital
National Defense Medical Center
Taipei, Taiwan

1 Fujii Y, Toyooka H, Tanaka H. Prophylactic antiemetic therapy with a combination of granisetron and dexamethasone in patients undergoing middle ear surgery. *Br J Anaesth* 1998; **81**: 754–6
2 Fujii Y, Tanaka H, Toyooka H. The effect of dexamethasone on antiemetics in female patients undergoing gynecologic surgery. *Anesth Analg* 1997; **85**: 913–7
3 López-Olaondo L, Carrascosa F, Pueyo FJ, Monedero P, Busto N, Sáez A. Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. *Br J Anaesth* 1996; **76**: 835–40
4 Fujii Y, Tanaka H, Toyooka H. Prophylactic antiemetic therapy with granisetron-dexamethasone combination in women undergoing breast surgery *Acta Anaesthesiol Scand* 1998; **42**: 1038–42
5 Henzi I, Walder B, Tramèr MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systemic review. *Anesth Analg* 2000; **90**. 186–94
6 Sehine I, Nishiwaki Y, Kakinuma R, *et al*. Phase II study of high-dose dexamethasone-based association in acute and delayed high-dose cisplatin-induced emesis: JCOG study 9413 *Br J Anaesth* 1997; **76**: 90–2
7 Italian Group for Antiemetic Research. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. *N Engl J Med* 1995; **332**: 1–5
8 Italian Group for Antiemetic Research Ondansetron versus metoclopramide, both combined with dexamethasone, in the prevention of cisplatin-induced delayed emesis *J Clin Oncol* 1997; **15**· 124–30

New insights into the regulation of erythropoietin production

Editor—We read the review by Jones and Wardrop on the measurement of blood volume in surgical and intensive care practice with interest.[1] We would, however, like to comment on their description of the regulation of erythropoiesis. The statement that erythropoiesis is regulated by haemoglobin concentration, arterial oxygen tension, haemoglobin–oxygen affinity and renal blood flow is only partly true. In particular, changes in renal blood flow do not usually alter erythropoiesis. An attractive model of regulation consistent with the data is that erythropoiesis is stimulated when there is an imbalance between the supply of oxygen to the renal interstitium and oxygen consumption by the renal tubule. The main determinant of oxygen consumption is tubular reabsorption of sodium, itself related to the glomerular filtration rate. Thus erythropoiesis is generally stimulated in anaemia and altitude hypoxia when oxygen supply is impaired, but glomerular filtration rate and oxygen consumption are unaffected. In contrast, in renal artery stenosis there can be a dramatic reduction in renal blood flow and so a large reduction in renal oxygen supply, but this does not increase erythropoietin secretion, neither in the clinical setting nor in experimental animals. According to the model, the reason for this is that a primary reduction in renal blood flow leads to a proportionate reduction in glomerular filtration and so a reduction in sodium reabsorption and oxygen consumption.

At the molecular level, Jones and Wardrop state that the oxygen sensor for erythropoietin section is believed to be a haem protein synthesized in the kidney and that the deoxygenated form of this protein stimulates the gene.[1] There have been a number of developments in this field since the publications they quote in their review.[2] The erythropoietin-producing cells have been identified as fibroblasts of the cortex and outer medulla.[3] Studies of gene regulation have led to the identification of a multiprotein complex (hypoxia-inducible factor-1, HIF-1), which binds specific DNA sequences termed 'hypoxic response elements', modulating expression of a range of target genes.[4] The HIF-1 complex contains two non-haem proteins (HIFα and HIFβ), members of the bHLH-PAS family of transcription factors. The regulatory elements are the α subunits, which are rapidly destroyed in normoxia. The precise mechanism by which oxygen destroys HIFα subunits is unknown and a 'molecular sensor' has not yet been identified, though oxygen-dependent production of reactive oxygen species has been suggested.[5] HIFs are emerging as major modulators of the vasculature, likely to be involved in embryonic development, in tissue ischaemia, in diabetic retinopathy, and in tumour angiogenesis.[6]

Whatever the sensing mechanism for hypoxia, what is interesting is that it probably operates in many, if not all mammalian cells. For example, it has recently been shown that von Hippel Lindau (VHL) tumour suppression protein is also necessary for the destruction of HIFα subunits.[7] In the absence of VHL protein, cells have high levels of α subunits, resulting in a 'hypoxic' phenotype and high levels of angiogenic growth factor, which might explain the angiogenic tumour characteristics of von Hippel Lindau disease. This observation also provides an insight into the genesis of sporadic renal carcinoma, as over 70% of clear cell cancers have VHL mutations.[8]

Perhaps the most exciting aspect of this field, which stems from physiological studies of erythropoiesis, is its therapeutic possibilities. It might be desirable to potentiate adaptive responses to hypoxia in ischaemic tissues, while in conditions such as diabetic retinopathy and tumour angiogenesis, blocking the response would be of benefit.

J. J. Pandit
Nuffield Department of Anaesthetics
John Radcliffe Hospital
Oxford

P. H. Maxwell
Wellcome Trust Centre for Human Genetics
Oxford

1 Jones JG, Wardrop CAJ. Measurement of blood volume in surgical and intensive care practice. *Br J Anaesth* 2000, **84**· 226–35
2 Goldberg MA, Dunning SD, Bunn HF. The regulation of the erythropoietin gene· evidence that the oxygen sensor is a haem protein. *Science* 1988; **242**: 1412–15
3 Maxwell PH, Osmond MK, Pugh CW, Heryet A, Nicholls LG, Tan

CC, Doe BG, Ferguson DJ, Johnson MH, Ratcliffe PJ. Identification of the renal erythropoietin-producing cells using transgenic mice. *Kidney Int* 1993; **44**. 1149–62

4 Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic double-helix-loop-PAS heterodimer regulated by cellular O_2 tension. *Proc Natl Acad Sci USA* 1995; **92**: 5510–14

5 Fandrey J, Frede S, Jelkmann W Role of hydrogen peroxide in hypoxia-induced erythropoietin production. *Biochem J* 1994; **303**: 507–10

6 Semenza GL. Regulation of mammalian O_2 homeostasis by hypoxia-inducible factor 1 *Ann Rev Cell Dev Biol* 1999; **15**· 551–78

7 Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, Wykoff CC, Pugh CW, Maher ER, Ratcliffe PJ. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature* 1999; **399**. 271–5

8 Gnarra JR, Tory K, Weng Y, Schmidt L, Wei MH, Li H, Latif F, Liu S, Chen F, Duh FM, Lubensky I, Duan DR, Florence C, Pozzatti R, Walther MM, Bander NH, Grossman HB, Brauch H, Pomer S, Brooks JD, Isaacs WB, Lerman MI, Zbar B, Linehan WM. Mutations of the VHL tumour suppressor gene in renal carcinoma. *Nature Genetic* 1994, **7**· 85–90

Measurement of blood volume

Editor—I read with interest the review on measurement of blood volume by Jones and Wardrop [1] The fundamental basis of intensive care practice is to detect, prevent, and correct tissue hypoxia. Fluid resuscitation for hypovolaemia is integral to this process and in many patients there is a difficult balance between volume replacement and inotropic support. Aggressive use of inotropes has been shown to increase mortality in critically ill patients,[2] whereas persistent positive fluid balance has been associated with poor outcome in ARDS.[3] Commonly used indicators of hypovolaemia are often insensitive[4] and therefore measurement of plasma volume is an attractive technique.

It was disappointing in the review that many of the techniques described have little relevance to bedside measurement of intensive care patients. Indocyanine green (ICG) can be measured easily *in vitro* by spectrophotometry[1] but can *also* be measured *in vivo* by reflection spectrophotometry.[5] A combined fibreoptic thermistor catheter is placed via a sheath into the femoral artery and advanced into the aorta. After a bolus injection of cold ICG into the right atrium, the concentration of dye is measured continuously. The time span of acquisition of data is 4–5 min, considerably shorter than with the serial blood sampling *in vitro* technique. This allows determination of circulating blood volume, intrathoracic blood volume (ITBV) and cardiac output using transpulmonary thermodilution. Circulating blood volume represents the compartment of total blood volume that contributes to ICG circulation during data acquisition. Although the two volumes are different there is an excellent correlation between them (r=0.87). The time scale of data acquisition means that the technique is much less sensitive to capillary leakage.

A further development is the use of ICG pulse spectrophotometry. Adaptation of the technique of pulse oximetry allows the non-invasive optical measurement in the patient's nose or finger of the arterial concentration of the dye.[6] Although prone to motion artefact, this method has an estimated error of less than 10% compared to conventional *in vitro* tests. ICG is rapidly cleared in patients with normal hepatic function allowing repeated measurements within 20 min at the bedside.

Finally, due to the large variation in circulating plasma volume, its value may be of little help in choosing between volume loading and inotropic support. Changes in central venous pressure and pulmonary artery occlusion pressure may also not indicate changes in right and left heart volume.[7] Intrathoracic blood volume has been shown accurately to reflect circulatory volume in critically ill patients.[8] Although ITBV can be measured using ICG as described above, it can also be estimated from global right and left heart volumes derived from standard transpulmonary thermodilution at the bedside.[9] Therefore, transpulmonary thermodilution using a central venous catheter and a femoral arterial catheter can give us information about not only cardiac output but also ITBV. All of this at the bedside with a single injection of cold dextrose!

M. J. L. Schuster-Bruce
Bristol

1 Jones JG, Wardrop CAJ Measurement of blood volume in surgical and intensive care practice. *Br J Anaesth* 2000; **84**: 226–35

2 Hayes M, Timmins AC, Ernest HS, Yau EHS, Palazzo M, Hinds CJ, Watson D. *N Engl J Med* 1994; **330**: 1717–22

3 Wyncoll DLA, Evans TW. Acute respiratory distress syndrome. *Lancet* 1999; **354**: 487–501

4 Hamilton-Davis C, Mythen MG, Salmon JB, Jacobson D, Shukla A, Webb AR. Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry. *Intensive Care Med* 1997; **23**: 276–81

5 Hoeft A, Schorn B, Weyland A, Scholz M, Buhre W, *et al.* Bedside assessment of intravascular volume status in patients undergoing coronary artery bypass surgery. *Anesthesiology* 1994; **81**· 76–86

6 Haruna M, Kumon K, Yahagi N, Watanabe Y, Ishida Y, *et al.* Blood volume measurement at the bedside using ICG pulse spectrophotometry. *Anesthesiology* 1998; **89**: 1322–8

7 Buhre W, Weyland A, Schorn B, Scholtz M, Kazmaier S, *et al.* Changes in central venous pressure and pulmonary capillary wedge pressure do not indicate changes in right and left volume in patients undergoing coronary artery bypass surgery. *Eur J Anaesthesiol* 1999; **16**: 11–7

8 Lichtwarck-Aschoff M, Zeravik J, Pfeiffer UJ. Intrathoracic blood volume accurately reflects circulatory volume status in critically ill patients. *Intensive Care Med* 1992; **18**: 142–7

9 von Spiegel T, Hoeft A. Should we measure plasma volume in intensive care? *Intensive Care Med* 1999; **25**: 1212–14

Editor—We have some sympathy with these views in the sense that, as pointed out in our review, the choice of methodology will be influenced by local facilities. A technique which is applicable entirely at the bedside is particularly attractive. However, there is still the concern that methods based on, or validated by those based on the volume of distribution of albumin are potentially flawed. Blood volume measurement based on the distribution of indocyanine green (ICG) follows closely that obtained using radiolabelled albumin.[1] Blood volume measured using albumin is closely correlated with that using labelled red cells.[2] As pointed out in the letter, there is an 'excellent correlation' between an easily determined derivative of blood volume and total blood volume—both based on the volume of distribution of ICG.[3] Everything therefore seems to be in order. However, in statistical terms a correlation between two methods, designed to measure the same thing, is hardly surprising and the test of significance 'is irrelevant to the question of agreement'.[4] Different methods should be compared by analysis of bias described by Bland and Altman.[4] This kind of analysis shows good agreement between blood volume, in healthy volunteers, measured with iodinated albumin and that determined by a non-invasive pulse dye-densitometry using ICG.[5] However, in the field of blood volume measurement, labelled red cells are considered to provide the 'gold standard' and the same statistical analysis shows an inconsistent bias between blood volumes determined, in a variety of patients, using iodinated albumin or red cells.[5] Hence, although correlated, the two measurements do not always agree. We are not aware of any data that measures agreement in this way between total blood volume, determined using red cells, and total blood volume, or any part of it, determined using ICG. Such data, combined with the obvious practicality of ICG, would provide the best of all worlds. However, until such data are available, the method is no better, or indeed worse, than most others.

G. Jones
C. Wardrop
Cardiff

1 Bradley EC, Barr JW. Determination of blood volume using indocyanine green (Cardio-Green) dye. *Life Sci* 1968; **7**: 1001–7
2 Thomas E, Jones G, de Souza P, Wardrop CJ, Wusteman FS. Measuring blood volume with fluorescent-labelled starch. *Crit Care Med* 2000; **28**: 627–31
3 Hoeft A, Schorn B, Weyland A, Scholz M, Buhre W, Stepanek E, Allen SJ, Sonntag H. Bedside assessment of intravascular volume status in patients undergoing coronary bypass surgery. *Anesthesiology* 1994; **81**: 76–86
4 Bland MJ, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **i**. 307–10
5 Iijima T, Iwao Y, Sankawa H. Circulating blood volume measured by pulse dye-densitometry. *Anesthesiology* 1998, **89**: 1329–35
6 Webb AR. Fluid management in intensive care—avoiding hypovolaemia. *Br J Intensive Care* 1998; **7**: 59–64

One-lung anaesthesia: the need for renewed respect

Editor—Drs Pennefather and Russell do well in their Editorial to draw attention to the risk of pulmonary morbidity following one-lung anaesthesia.[1] They refer to a recent report published in The National Confidential Enquiry into Perioperative Deaths (NCEPOD), which analysed 78 questionnaires relating to perioperative death during or following oesophagectomy.[2] This report and the numerous studies that have identified less than optimal double-lumen tube (DLT) placement when performed without the aid of fibreoptic bronchoscopy, lead the authors of the Editorial to conclude that fibreoptic bronchoscopy should be used at DLT placement, following patient re-positioning and, if required, during surgery. They state that 'fibreoptic bronchoscopy is the only technique available to detect anatomical variability and pathological distortions', and conclude by questioning how much longer will it be considered 'defensible' to conduct one-lung anaesthesia without the use of fibreoptic bronchoscopy.

We would like to dispute their statement on the assessment of bronchial anatomy and pathology, and we worry about the implication that the use of fibreoptic bronchoscopy should be considered mandatory. We regularly perform rigid bronchoscopy and assess bronchial anatomy/pathology immediately prior to DLT placement, and we do not believe that an experienced thoracic team should cancel or defer commencing a thoracic operation if the available fibreoptic bronchoscopes are being used in other operating theatres, as occasionally occurs in our hospital. So-called 'blind placement' should in fact imply a 'functional visualization' of tube position. By comparing peak and plateau inflation pressures and tidal gas movement in the two lungs, the experienced thoracic anaesthetist should be able to visualize in his or her mind's eye where the bronchial cuff is positioned. This comparison is performed against the background of one lung being bigger than the other, one being dependent and the other non-dependent, and one, usually the non-dependent lung, often containing or being affected by the underlying pathology. An awareness of the signs of 'functional malplacement', and experience in accurately interpreting these signs, are essential Dislodgement or partial dislodgement of the DLT does occasionally occur in the course of surgery and should be diagnosed immediately on clinical grounds and not by fibreoptic bronchoscopy. In some emergency situations, experience with 'blind placement' may be of greater value than experience with (and dependence upon) fibreoptic placement. Unquestionably, the trainee anaesthetist should gain experience with both.

With regard to the high incidence of problems during or following one-lung anaesthesia for oesophagectomy, the trainee and occasional thoracic anaesthetist should know that in these cases there is an especial need for fibreoptic confirmation and/or experienced 'functional visualization'. With oesophagectomy, the delay between the placement of the DLT and the opening of the thoracic cavity means there is also a delay in both the onset of single-lung ventilation and the viewing of the lung in the open thoracic cavity. The experienced thoracic anaesthetist will not wait until the onset of single-lung ventilation to identify a DLT malplacement affecting the ventilated lung, or until the chest is opened and the surgeon reports an already collapsed upper lobe or, alternatively, upper lobe or whole lung hyperinflation. In this regard, the NCEPOD report makes a further valid comment that, 'Correct placement of a double lumen tube requires practice and is more likely to be achieved by the anaesthetists who use them regularly. For some anaesthetists, when working with a general surgeon who has a small oesophageal practice, this experience is acquired slowly'. This message may well apply even when fibreoptic bronchoscopy is used to assist DLT placement.

In the past, many anaesthetists have been reluctant to consider that the use of a DLT may have played a part in the development of respiratory complications following surgery. It is to be hoped that the recent NCEPOD report[2] and this Editorial[1] will serve to engender a renewed respect for the potential hazards of one-lung anaesthesia.

J. Pfitzner
Department of Anaesthesia

M. J. Peacock
Thoracic Surgical Unit
North Western Adelaide Health Service
Adelaide, South Australia

1 Pennefather SH, Russell GN. Placement of double lumen tubes–time to shed light on an old problem. *Br J Anaesth* 2000; **84**· 308–10
2 Sherry K. Management of patients undergoing oesophagectomy In· Gray AJG, Hoile RW, Ingram GS, Sherry KM, eds *The Report of the National Confidential Enquiry into Perioperative Deaths 1996/1997.* London: The National Confidential Enquiry into Perioperative Deaths, 1998; 57–61

Editor—Thank you for the opportunity to reply to Pfitzner and Peacock. We agree that blind placement of double lumen endobronchial tubes (DLEBTs) is a useful skill to acquire and teach our specialist registrars how to place a variety of DLEBTs blindly. However, we require our registrars to check and recheck the position of blindly placed DLEBTs with fibreoptic bronchoscopy (FOB); this assists in learning to blindly place DLEBTs. Most registrars need no further convincing that FOB should be used in all patients.

We too regularly perform rigid bronchoscopy to assess bronchial anatomy/pathology immediately prior to DLEBT placement. This is however, in our opinion, no substitute for FOB confirmation of accurate DLEBT placement. As discussed in our Editorial numerous studies have shown that it is not possible to accurately place all DLEBTs utilizing 'experienced functional visualization' alone. Klein and colleagues,[1] for example, studied 200 patients in whom DLEBTs had been blindly placed. During their initial FOB, functionally significant malplacement was detected in 25 cases despite normal 'functional visualization'.

We agree that the successful use of FOB to accurately position all DLEBTs and bronchial blocker requires experience. This is another reason to use a FOB in all patients. The decision to defer or cancel an operation because of the non-availability of monitoring equipment is always a balance between the risks of delay and the increased risks of proceeding.

S. H. Pennefather
G. N. Russell
Liverpool

1 Klein U, Karzai W, Bloos F, Wohlfarth M, Gottschall R, Fritz H, Gugel M, Seifert A. Role of fibreoptic bronchoscopy in conjunction with the use of double-lumen tubes for thoracic anesthesia: a prospective study. *Anesthesiology* 1998; **88**: 346–50

Placement of double lumen tubes

Editor—We read with interest the editorial on placement of double lumen endobronchial tubes (DLEBT)[1] and welcome the opportunity to comment, based on our local experience. We use a fibreoptic bronchoscope for all our cases, and teach and encourage our trainees to do the same.

Pennefather and Russell[1] point out that with the limited number of sizes of DLEBTs available and the significant variation in tracheobronchial anatomy and pathology, a reliable method of predicting the correct size tube for an individual patient remains to be found. Our own studies have demonstrated that methods based on measuring airway diameter from the preoperative chest radiograph[2] and computer tomographic scan,[3] although helpful in small patients, remain unsatisfactory. It is not uncommon in our population to be faced with an adult woman weighing less than 45 kg for thoracoscopic procedures. The introduction of the size 32F DLEBT has been very helpful. We agree than with the availability of small diameter fibreoptic bronchoscopes the opportunity to tailor the correct size of DLEBT is much improved, provided the manufacturers are responsive to our requirements.

Cost is an issue but so is practicability; the use of battery operated scopes (LF-DP, Olympus and F1-10P2, Pentax) allows us to save some cost and dispense with the cumbersome light source. Another excuse put forward for not using the fibreoptic scope routinely is that it takes time. Cheong and Koh[4] have demonstrated that with practice, quick and accurate placement is possible if the scope is used at the outset. This method is all the more important in emergency cases such as bronchopleural fistulae, when a rapid sequence induction is required[5] and isolation is crucial.

It is tempting to infer that fibreoptic bronchoscopic confirmation of endobronchial tube placement may have reduced the mortality reported in the recent national confidential enquiry into perioperative death (NCEPOD) following oesophagectomy.[6] Continuous exposure, monitoring clinical signs including capnography[7] and a team approach remain the cornerstone in managing this condition. Indeed there may be situations where the use of a fibreoptic bronchoscope is inappropriate, such as in pulmonary haemorrhage.[8]

We welcome the NCEPOD report,[6] which highlights the mortality and morbidity associated with malpositioned double-lumen tubes. Our departmental critical incident reporting system which in turn forms part of the Australian Incident Monitoring Study (AIMS) has so far failed to report any similar problems. In the 2000 cases of tracheal intubations reported by AIMS, only four cases involved malplacement of DLEBT.[9] It was not mentioned if fibreoptic bronchoscopic checking was performed for these cases. In the more recent AIMS report of 5000 cases, the use of DLEBT was not implicated in the cases of aspiration.[10] Thus routine use of the fibreoptic bronchoscope has met with resistance from some of our 'experienced' colleagues who advocate reliance on clinical signs alone,[11] and others who use the fibreoptic scope as a backup.

M. Y. H. Chow
P. C. Ip-Yam
Singapore

1 Pennefather SH, Russell GN. Placement of double lumen tubes—time to shed light on an old problem. *Br J Anaesth* 2000; **84**: 308–10
2 Chow MYH, Liam BL, Lew TWK, Chelliah RY, Ong BC. Predicting the size of a double-Lumen endobronchial tube based on tracheal diameter. *Anesth Analg* 1998; **87**: 158–60
3 Chow MYH, Liam BL, Thng CH, Chong BK. Predicting the size of a double-lumen endobronchial tube using computer tomographic scan measurements of the left main bronchus diameter. *Anesth Analg* 1999; **88**: 302–5
4 Cheong KF, Koh KF. Placement of left-sided double-lumen endobronchial tubes: comparison of clinical and fibreoptic-guided placement. *Br J Anaesth* 1999; **82**: 920–1
5 Ip-Yam PC. Placement of double-lumen endobronchial tubes. *Br J Anaesth* 1999; **83**: 682–3
6 Sherry K. Management of patients undergoing oesophagectomy. In Gray AJG, Hoile RW, Ingram GS, Sherry KM, eds. The Report of the National Confidential Enquiry into Perioperative Deaths 1996/1997. London: *The National Confidential Enquiry into Perioperative Deaths*, 1998; 57–61
7 Ip-Yam PC, Innes PA, Jackson M, Snowdon SL, Russell GN. Variation in the arterial to end-tidal $P\text{co}_2$ difference during one-lung thoracic anaesthesia. *Br J Anaesth* 1994, **72**: 21–4
8 Ip-Yam PC, Van Heerden N, Wright G. Anaesthesia for aortoesophageal fistula. *Anaesth Intens Care* 1993; **21**: 450–2
9 Szekely SM, Webb RK, Williamson JA, Russell WJ. Problems related to endotracheal tube: analysis of 2000 Incident Reports. *Anesth Intens Care* 1993; **21**: 611–6
10 Kluger MT, Short TG. Aspiration during anaesthesia: a review of 133 cases from Australian Incident Monitoring Study (AIMS). *Anaesthesia* 1999; **55**: 19–26
11 Brodsky JB. Fibreoptic bronchoscopy should not be a standard care when positioning double-lumen endobronchial tubes. *J Cardiothorac Vasc Anesth* 1994; **8**: 373–7

Identifying tracheomalacia–an alternative approach

Editor—Dr Sinha and colleagues should be congratulated for highlighting the danger of tracheomalacia following thyroid surgery.[1] Tracheal collapse may be both insidious and delayed, so correct identification of patients at risk is vital.

We adopt a different approach. Following a successful pilot study in 1991, we have used the laryngeal mask airway (LMA$^{®†}$) to maintain airway patency during thyroid and parathyroid surgery.[2]

Our original motivation was to aid location of the recurrent laryngeal nerve. The LMA® permits fibreoptic inspection of vocal cord movement in response to electrical stimulation of the recurrent laryngeal nerve. Furthermore, the integrity of the nerve may be confirmed prior to surgical closure. Hobbiger reported our experience of 97 cases.[3]

In addition, we feel that the LMA® may also facilitate assessment of the risk of tracheomalacia. Prior to surgical closure, residual neuromuscular blockade is reversed and propofol infusion adjusted so that spontaneous respiration is reestablished. The trachea may be inspected and palpated without the 'splinting' effect of an endotrachial tube. Moreover, the LMA® permits fibreoptic inspection of the trachea for evidence of collapse during inspiration. If tracheal patency appears compromised, a tracheostomy may be created under controlled conditions whilst the patient remains anaesthetised. Palazzo recently described this approach in a series of six patients at high risk of tracheomalacia.[4]

We, like Dr Sinha and colleagues, feel the dangers of tracheomalacia have been underemphasized. We believe our alternative approach may offer significant advantages.

K. Moaz
R. A. Greatorex
J. G. Allen
Queen Elizabeth Hospital
King's Lynn
Norfolk

†LMA® is the property of Intavent Limited

1 Sinha PK, Dubey PK, Singh S. Identifying tracheomalacia. *Br J Anaesth* 2000; **84**: 127–8
2 Greatorex RA, Denny NM. Application of the laryngeal mask airway to thyroid surgery and the preservation of the recurrent laryngeal nerve. *Ann R Coll Surg Engl* 1991; **74**: 966–7
3 Hobbiger HE, Allen JG, Greatorex RA, Denny NM. The laryngeal mask airway for thyroid and parathyroid surgery. *Anaesthesia* 1996; **51**: 972–4
4 Palazzo FF, Allen JG, Greatorex RA. Laryngeal mask airway and fibreoptic inspection in thyroid surgery: a method for timely identification of tracheomalacia *Ann R Coll Surg Engl* 2000, **82**: 141–2

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Book Reviews

Problems in Anaesthesia Series. *Obstetric Anaesthesia.* L.A. Fleisher and D.S. Prough (editors-in-chief) A.M. Bader and S Datta (guest editors). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 131; indexed; illustrated. Price US$52. Like the curate's egg, this book is good in parts. The fly leaf of this volume of the quarterly *Problems in Anaesthesia* series says of itself 'This outstanding quarterly journal sheds light on difficult and evolving areas . . . (it) provides the knowledge and expertise of specialists, guest edited by an expert, (and) focuses on developments, complications and technological advances'. This is quite a challenge, for much is expected when many of the writers of this slim volume come from Harvard Medical School.

The volume is in 11 chapters, and each chapter has a useful summary of contents. The chapters are arranged in a logical order, and the cover of this anaesthetic subspeciality is comprehensive although there is some duplication. The book could do with more judicious editing, referencing and updating.

Some chapters are excellent. For example, the topical chapter by Scott Segal unravels the difficulties of studying the complex effects of epidural analgesia on the method of delivery. The chapter on local anaesthetics is also clear and up to date, and includes the concept of chirality. However, a paragraph on EMLA and young children is out of place in this book, and the paragraphs on chirality and the use of adrenaline in epidural local anaesthetics are duplicated in the next chapter on anaesthesia for delivery. That chapter has several paragraphs on the use of narcotics for maternal pain relief, but there is no mention of the effects of narcotics in slowing gastric emptying.

The section on how to do an epidural would be more in place in a textbook on obstetric anaesthesia. It is stated that 'modern techniques (of analgesia) allow parturient patients to enjoy pain-free delivery with minimal maternal or neonatal side effects'. This is at odds with the following excellent chapter by Segal, which shows that epidural analgesia may indeed alter the method of delivery.

This is an American book and so, in the chapters on anaesthesia for Caesarean section, it is good to see included several British references as well as American ones suggesting that regional analgesia has proved safer than general anaesthesia for Caesarean section. However, the majority of the references are quite old. The chapter on physiological adaptations of pregnancy is well written, but the fascinating tables on the cardiovascular and respiratory changes have no references.

This book could be titled as an 'American' or the 'Harvard Synopsis of Obstetric Anaesthesia'. It is readable, concise and quite good value at US$52 (about £35). Reading it would inform UK anaesthetists both at the Consultant and Specialist registrar level of the activities of our American cousins in this anaesthetic subspeciality.

J. Sprigge

Psychological Mechanisms of Pain and Analgesia. Donald D. Price. *Progress in Pain Research and Management Volume 15.* Published by IASP Press, Seattle. Pp. 248; indexed; illustrated. Price US$69. ISBN 093109229.

Q. When is the stimulation of nociceptors pain and not pain?

A. When it is considered unpleasant and associated with potential tissue damage, but not when associated with pleasant sensations such as eating capsaicin in tacos (cooking instructions supplied). Thus Donald Price introduces the fundamental problem of personal evaluation of pain perception. This book devotes nine chapters to a highly academic exploration of the physiological and psychological characteristics of nociception from the peripheral to the central processes in the pain experience. It is to date the most comprehensive volume in an accessible form It includes PET studies with clearly reproduced pictures of brain slices showing the structures and calculations involved in identifying increasing brain regions recruited to process increasing stimulus intensity.

Throughout the book, Price explains in detail and from a number of different view points, that pain processing differs radically from the claim that it is subserved by exclusive neurons and pathways that project to discrete centres in the brain. Indeed, he is able to demonstrate that the areas involved in the neural imaging studies are not exclusively dedicated to pain processing, but become recruited as a function of peripheral or central sensitisation. Pain needs to be comprehended as both a somatosensory and an affective experience, both of which are subserved by different mechanisms. Price shows evidence that nociceptive stimuli activate neural pathways having direct input to areas of the brain responsible for the production of fear arousal, but that there is also a secondary stage of affective evaluation which engages the cortical areas of the brain likely to be involved in emotional reactions and the planning of behavioural responses, thus diverting attentional and motivational resources away from other activities.

The complicated business of measuring such a subjective experience is given a whole chapter in which the emotional responses are specified into five different areas. An interesting study is quoted in which all five are measured with separate VASs under different conditions of pain and clearly demonstrate the different contributions of anger, fear, depression, frustration and anxiety depending on the circumstances in which pain is experienced. For example, lower back pain is associated with relatively high levels of all the negative emotions, especially frustration, whereas labour pain is associated only with elevations in anxiety. If chronic pain is multidimensional then its assessment needs separate measures of nociception, immediate pain related affective disturbance, suffering and overt pain behaviour. Price sets out criteria for the reliable measurement of these several factors. He concludes that VAS measurements may be the most efficient way of achieving this.

Other chapters focus on the relative contribution of conditioned responses and expectancy in placebo analgesia and the mechanisms of hypnotic analgesia This, he concludes, can modulate both the affective dimension of pain and the sensation intensity differentially by targeting meaning and sensation with different suggestions. The anterior cingulate cortex and the primary somatosensory area are shown to be activated differentially, in parallel with changes in subjective reports of unpleasantness and intensity separately under the different conditions of hypnotic suggestions. This chapter ends with speculation about the far reaching implications for hypnosis in the treatment of pain if both aspects are adequately addressed, especially as hypnotic ability may not be a critically limiting factor.

The chapters each stand alone as separate papers on the relevant aspects, and as such tend to be repetitive if approached at a single sitting, especially as Price's agenda is clearly on emphasizing the importance of the personal meaning of pain. However, the concluding chapter helpfully summarizes the research quoted in the foregoing pages.

This book is dense with experimental data and is by no means an introductory text. However, it is a 'must have' for those who

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are interested in researching the most recent and comprehensive theories of pain and its management.

K. Fisher

Perioperative Care of the Eye Patient. G. Vafidis, P.N. Robinson and G.M. Hall. Published by BMJ Books, London. Pp. 70; indexed; illustrated. Price £10.95. ISBN 0727912259.

This is a useful yet concise book on perioperative care of the ophthalmic patient. It indicates in its introduction that it outlines the components of care in the perioperative period that reflect current practice, with emphasis on day stay procedures, and indeed it achieves its aim. The book contains 12 chapters that take the reader from surgical decisions in the outpatients department, through all aspects of anaesthesia and surgery, to dealing with complications when patients are discharged to the community. It is presented in a logical manner and in a way that is easy to read and to understand. Important points such as preoperative assessment and management of specific problems such as diabetes, hypertension and anticoagulation, are clearly discussed. The book has 52 tables which summarize various indications and contraindications as well as the advantages and disadvantages, of regional and general anaesthesia. It also describes the different types of regional anaesthetic techniques in a simple and easy to understand way. It has a chapter on care of the paediatric patient which highlights paediatric anaesthetic problems and postoperative care. Moreover, there is a very useful chapter that deals with perioperative crises such as anaphylaxis, cardiac arrest, malignant hyperthermia, and brain stem anaesthesia following regional anaesthesia. I liked the chapters on the Recovery Unit, Fitness for Hospital Discharge, and Care in the Community.

However, the book has only three photographs related to local anaesthetic techniques. There are no diagrams to demonstrate frontal views, or the site and direction of needles used to perform regional anaesthesia. Furthermore, the authors fail to mention the importance of the size, type and length of the needle used for regional anaesthesia of the eye. The advantages and disadvantages of using epinephrine-containing local anaesthetics in the eye are not mentioned.

In the chapter on general anaesthesia, the authors give only a single line statement about consent from patients. Considering that the majority of eye patients tend to be aged and many of them are either confused or suffer from dementia, I would have thought that this particular item would merit more space in such a book.

The authors discuss the risk of aspiration of stomach contents and devote a table to management of tracheal intubation when there is such a risk. This is an important area the management of which deserves more detail as some of the drugs suggested by the authors, for example, metoclopramide, which raise intraocular pressure, would not be used by all ophthalmic anaesthetists. The advantages and disadvantages of using succinylcholine or non-depolarizing neuromuscular blocking drugs, and how to use them, for example, the use of a priming dose of a non-depolarizing muscle relaxant, also deserve a mention. There is little information about the pharmacology of individual anaesthetic agents and their effect on the eye or the effect of various techniques used perioperatively, for example, tracheal intubation or insertion of a laryngeal mask airway, on intraocular pressure; these are gaps that should be filled. The authors do not mention the need to avoid succinylcholine in patients undergoing surgery for the correction of squint, or make a distinction, in terms of preparation or management, between different paediatric age groups. The section on monitoring during surgery, although adequate, lacks information on monitoring of mechanically ventilated patients. Furthermore, reliance on trained technicians to monitor patients during regional anaesthesia is, in my view, not helpful in enhancing the role of the anaesthetist in the management of the ophthalmic patient.

The authors suggest that this book would enable all members of the team, from consultants to operating department practitioners, to enhance patient care. I agree that the book goes some way to achieving this, particularly for the anaesthetist or surgeon in training. However, at consultant level the book does not offer that extra value. But I certainly recommend it to specialist registrars as a handy book that is easy to read and assimilate.

S.M. Mostafa

International Anesthesiology Clinics. W.E. Hurford (editor-in-chief). Vol. 38: Number 1: 2000: *Thoracic Anesthesia/Hyperbaric Medicine.* P.F. Dunn and P. Barach (editors). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 174; indexed; illustrated. Price US$66.

This literary stable, now breeding its 38th volume, has responded to the new millennium with a proposal to produce issues that cover, on occasion, two separate topics. With this process, it is hoped to produce review and debate at the pace associated with journals. It is a challenging concept, not least for reviewers; for, as in this case, one topic is likely to fall into a field that can be reviewed with some authority and the other has to be assessed from the perspective of an initiate. At first glance, the pairing of thoracic anaesthesia with hyperbaric medicine is odd, but it should work, principally, because both topics are brimful with respiratory physiology and oxygen pathology.

The thoracic anaesthesia section is of four chapters; an eclectic mix of hot and cold topics: management of the emphysematous, the physiology of one lung ventilation, tracheal resection, and small airways disease—referred to as the bronchospastic.

Emphysema, a quintessential condition of the third age of thoracic anaesthesia, is the subject of a wide-ranging but unfocused discussion. As in the succeeding chapter, the understood and basics are well reviewed but the remit is interpreted too widely: the writers have been made vulnerable to criticism by straying into areas where the lack of front-line experience becomes evident. After reading, could one anaesthetize a patient with emphysematous bullae as a co-morbidity? No, not safely. Could one anaesthetize a patient with emphysema for lung transplantation or lung volume reduction surgery? No, not successfully Preoperative conditioning, optimization and right ventricle function assessment get scant and belated consideration. There is adequate emphasis on the attention to detail necessary to ensure expiration is optimum; and on the cost, in terms of physiological compromise. Warnings about dynamic hyperinflation and positive pressure ventilation are present but well hidden, under induction of anaesthesia. But there is no information about premonitory clinical signs, such as pulse oximetry paradox, that harbinger this potentially fatal condition, and which can present late during surgery, notably when airway management of ventilator changes are implemented. A grave omission is the absence or information about the effects and management of the differential lung compliance situations created by single lung transplantation. Referencing is patchy; that on lung transplantation is inadequate

The physiology of one lung ventilation and the lateral decubitus position is always going to be the key to the form of any references on thoracic anaesthesia. Unfortunately, this rendering is handicapped by a baggage of detail about placement of double lumen tubes, which is, typically, didactic, and bears many hallmarks of not being tested robustly enough by those who promulgate it to have experienced that it is not failsafe. We are informed that 'one lung ventilation was originally performed to prevent infectious spillage from one lung to the other'. At the very least, writing it should have made the authors think about advocating the inflation of the tracheal cuff of a double lumen tube first, if the other lung, that is going to be uppermost, is the source of spillage–but it did not. North American commentators have blinkers on for the inherent design faults in plastic tubes. Many of the problems with double lumen tubes are because the plastics industry will not or cannot replicate features of the red rubber antecedents. Commercial considerations have left these uncorrected and largely unchallenged, so that a mythology (mandatory diagnostic fibreoptic bronchoscopy), mystique and manufactured science have been allowed to build up around the art of their use. Just look at a Gordon Green endobronchial tube (respectable size upper lobe slot, that expands on inflation of the cuff) or a Robertshaw tube (limited tracheal length, endobronchial bevel direction) to obtain some idea of how the fabric of this section becomes corroded. I have digressed–on a hobby horse. The science is quite well dealt with but it is uncritical, with old formatting of topics and very tired referencing. It is turgid. One page has the acronym PEEP on it no less than 28 times. Such discourses would be so much easier to read if authors realized that unless the taught have complex concepts presented in a simple way, they become confused, bumble, talk gibberish and fail examinations. This topic can be made more simple, and more relevant in the context of routine practice, by recognizing the great conspiracy of one-lung anaesthesia. It is against the functional residual capacity of the dependent lung. The cavalry, coming to rescue it from its anatomical, physiological and surgical siege, is forced to traverse a 30 cm tube which, to be frank, is usually (in a double lumen tube) smaller in diameter than the average adult urethra!

A thoroughbred: the chapter on tracheal surgery. Even the most experienced tracheal surgeon will only see a handful of these cases in a lifetime, and the same is true of their anaesthetic partners. The recognition that the fundamental skill is in rigid bronchoscopy, and that anaesthesia for it is the key, is something I applaud. Though I would not value gaseous induction as highly as the writer, I would not disagree in principle, as the method described is designed to minimize the hazards of provoking coughing fits and spasms–something that can be fatal in those already critically compromised by any form of central airways obstruction. The final chapter in this section is a cameo by the editor-in-chief. It is a workmanlike piece on dysfunctional airways with sound sense on recent thought, evidence, experience and therapy. Shame about perpetuating the corrupt and unfortunate word 'bronchospastic'.

The hyperbaric medicine section is a superb presentation marred only by the chapter of most importance to the practising anaesthetist. The subjects brought in under the umbrella of the topic are in fact of great import to all walks of anaesthetic life, even in their leisure: ischaemia–reperfusion, bubbles, gas embolism, decompression illness, crush injury, gas poisoning, oxygen toxicity, aviation and diving medicine. At the pace of an academic gallop, it makes for a fascinating read. It is a comprehensive and excellent starting point of reference into this myriad of conditions. A good way, too, for the examination candidate to get a sideways look at pulmonary physiology and the ever-expanding world of inflammation cascades. Amazingly, there are enough of some pathologies in the USA, such as carbon monoxide poisoning from car exhaust fumes, for the conduct of controlled trials. But the results are equivocal. On most, there are still stewards' enquiries, and on some the inconclusive conclusion is that hyperoxia may do more harm than good. All this science needed to be relevantly summarized for the proposed readership. Do my patients need access to a high pressure chamber? What is the demand, and would the demand justify the resources? What would happen to my patient on referral and how could I help to ensure it was a safe process? Instead, illustrated with grainy photographs which contribute little, is a rather irritating homily on intensive care (including the need for ethicists) that should be taken as read. As should the section on the transport of the critically **'Ill'** (the unfortunate use of a font that does not distinguish upper case 'i's from 'l's). It failed to distinguish, incisively, circumstances of transfer in a vehicle on wheels at ambient pressure from those of locking an equally obtunded and unconscious patient inside a metal box and ratcheting up the pressures to unphysiological levels. Is the target readership so simple that it has to be informed, not just once but twice, that Luer fittings should be used so that inadvertent line disconnections do not occur; or that heparin saline should be used as line-flush? Filling the tracheal tube cuff with saline is mentioned, but surely this essential manoeuvre warrants more than one sentence-justification and a few references? Other than knowledge about the requirement for myringotomies, does the readership need to be told how to do them? All that fascinating science on bubbles and no word of what happens if some go walkabout from the arterial and venous monitoring lines in the unconscious patient entombed in a monoplace chamber. And any rate, how reliable is the intelligence from monitoring once the whole body is squeezed as though in a sub-marine vice? I still do not know and I have read it twice!

On balance, this volume will probably stay on the library shelf to maintain continuity in the series. I recommend an occasional dusting – by a specialist – of the chapter on tracheal surgery; by a trainee of the science and research in hyperbaric medicine. This foal has fallen at the first jump. It could yet come good, but it must have more authority and, given the series title, preferably an international one. If it follows this pattern of breeding out of one-towns' studs, there will be more nags than thoroughbreds. Methinks not even enough curates' eggs at this Bostonian Tea Party!

I.D. Conacher

Review of Intensive Care Medicine 2nd edn. N.A. Smyrnios, R.S. Irwin, F.B. Cerra and J.M. Rippe (editors). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 275. Price US$49.95. ISBN 0-7817-2021-4.

This book is written to accompany its parent book, the 4th edition of *Irwin and Rippe's Intensive Care Medicine* (Lippincott, Williams and Wilkins, Philadelphia 1999). As a review it is essentially along the format of multiple choice questions (MCQ) and answers. It follows the chapter layout of the parent text and the reader is often encouraged (naturally) to avail of this resource! Indeed, as such it is a scarce entity given the paucity of intensive care MCQ books directed at the trainee in the British Isles.

The book is aimed at the resident in training for board certification in the United States. The format of the questions varies as expected with 'true and false', 'select the true/false statement', 'matching' and 'select the best answer' options, the latter being the most prevalent by far. Only the first format, stem with true/false options, is in widespread use in collegiate examinations in the British Isles. My preference for MCQ books is for the answers to be on the page opposite or overleaf as using multiple bookmarks can be frustrating, especially when you read in error the answer to the next question! The text and questions are clear and well written and I was happy in general to *agree to differ* with some of the suggested correct answers on occasion.

The topics covered are comprehensive and include some welcome ethical and medico-political aspects of the provision of critical care. An appendix has been *appended* to the end of the book that includes the usual pharmaco-physiological formulae and I suppose one should not look the gift horse in the mouth. However, there are some errors in some of the formulae, probably related to oversights in proof reading, and some tables may need updating. Also there is no table to allow conversion of units to *Système Internationale*. My favourite section is missing in that there is no index – *understanding a comprehensive index indicates* *a comprehensive understanding*! Whether it is practical to include one in an MCQ book is debatable, but it allows one to quickly find out if the latest topics are included and serves to test the reader's familiarity with the contents.

This book will no doubt appeal to trainee intensivists in the USA, especially those who have already purchased the parent book. However, the relevance of this book to the British Isles trainee intensivist will be somewhat limited, not necessarily by the limitations of the book itself, but by the fact that there is currently no MCQ examination as yet for Intercollegiate Board accreditations! This may account somewhat for the aforementioned paucity of similar publications. In the current drive to continuing professional development and clinical governance it may appeal to some practising intensivists. Whilst I found the book quite useful and interesting, it is at present a lower priority purchase.

M.O. Columb

Safety in Medicine. C Vincent and B De Mol (editors). Published by Elsevier Science, Oxford. Pp. 268, indexed; illustrated. Price US$99. ISBN 0-08-043656-0.

This is a book arising from the 16th workshop of NeTwork (sic) held in 1998, on Safety in Medicine, each chapter co-authored by one of the participants. It seeks to apply models of safety derived from industry to the practice of medicine, drawing many of its illustrations from anaesthesia, though none of the authors is an anaesthetist. One is thus, as a practising anaesthetist, in a position comparable to a stone age tribesman reading a report by an anthropologist on some of his activities. It is somewhat discouraging, therefore, for this tribesman to discover failures of understanding of the role of his tribe in the jungle of medicine. For example, one author thinks that the anaesthetist is part of the surgeon's team, another (this is cardiac surgeon, so perhaps less surprising, though no less culpable) who fails to include in his list of the anaesthetists' roles the maintenance of anaesthesia, and a third who thinks surgeons and anaesthetists come from different professions (are surgeons doctors?) Similarly, there is implicit criticism for the division of hospital medical effort into teams, these being either at war or in armed truce, while failing to realise the industry ideal of a single functional team is not realisable in medicine because each team's responsibility is too complex for any ordinary professional to be able to lead more than one It is rather insulting to assume, as this author seems to, that this model of work is a mistake rather than the least bad system that can be found. This book also has, as so often in multi-foreign author works, one chapter in which, though all the words are English, the language somehow is not, and an index where subjects are referenced only to chapter numbers, while names are referenced to the specific page, thus breaking new ground for the enhancement of the academic ego!

Let me not be too negative about this book, however. There are many fascinating insights into the world of error revealed in the examples. Thus we learn that one of the reasons for the failure of the Bjork-Shiley convexo-concave heart valve was drug and alcohol abuse among factory workers during manufacture, and the main problem with waiting for valves to fail before replacing them (the 'Run-for-your-life option') was that though patients/relatives correctly and instantly diagnosed valve failure, they were ignored by the 'experts'.

This last example illustrates the concept of 'Close Coupling' in accident analysis, where accidents are made more likely when the undesired outcome follows closely on the error. There is a good deal of analysis of theory of accidents using famous examples, and I learnt a lot about Zeebrugge. There are attempts to apply this to medicine, but in spite of numerous models, there is little success. There is praise for critical incident discussion, largely because it recognizes the possibility of error, which is sadly rare in medicine outside anaesthesia.

Finally, this book points out that while there is some truth in the analogy of anaesthesia to flight, medicine is less like the rule and routine based culture of civil aviation and more like military action. We act less like production chemists, more like knights errant, dashing off to rescue the patient in distress. In part, of course, this is because as with military action, our every patient is different. It is, however, tellingly pointed out that even the valiant knight needs to take time to tighten the girth, check the horse's shoes, and consider whether he can see potholes in the road through his newly designed helmet

The book is interesting for those with an interest in accidents both generally and in medicine, and it will open the general reader's eyes to new ways of thinking about our work. It would be wrong of me, however, to suggest it has a place on the average anaesthetic department's bookshelf

C.P.H. Heneghan

Handbook of Preoperative Assessment and Management B Sweitzer (editor). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp 459; indexed. Price £25 ISBN 0-7817-1633-0.

It was with considerable curiosity that I opened this book on preoperative assessment and management–a handbook identical in shape and size to the excellent *Clinical Anesthesia Procedures of the Massachusetts General Hospital*. For what reason could preoperative assessment have been detached from the remainder of anaesthesia?

The preface gives only indirect hints. It states that the book is written 'for clinicians interested in performing high-value preoperative assessments'. Further, a case for consensus should be 'formulated on an evidence-based perspective and expert opinion'. There is a need for 'a reference source' for 'state-of-the-art preoperative assessment curricula' This word curriculum implies the foundation for a course or an examination Would anaesthetists attend a course solely on preoperative assessment? The fact that the editor acknowledges a gap 'between best and actual practices' does suggest that such a need is perceived, at least by the authors.

However, as one reads further, it becomes apparent that this book is not written exclusively for anaesthetists. The generic terms 'clinician' and 'caregiver' seem to have been chosen deliberately In addition to anaesthetists, it seems that this book is aimed at surgeons, primary care providers, nurses, health care institutions, quality-assurance bodies and, indirectly, for the consumption of insurance companies. Does this mean that anaesthetists have abnegated their responsibility for preoperative assessment to others? Authors of several chapters acknowledge that 75–80% of surgery in the USA is now undertaken on a 'same-day' admission basis, that this policy is driven by the insurance companies, and that the anaesthetist 'no longer has guaranteed access to the patient'.

There are 20 chapters by 29 authors, several of whom are eminent in their fields. Thirteen chapters cover standard clinical issues, the range of conditions likely to influence anaesthesia, and how to conduct relevant assessments. In general, they are well written and up to date, although there is considerable variation between chapters in the number of references appended. Most are from journals, although some authors only quote from books In either case, the references are almost exclusively American. At the beginning, Michael Roizen gives an excellent summary of evidence against the routine performance, in otherwise fit patients having minor and intermediate surgery, of batteries of preoperative laboratory tests. In the last chapter, four case studies are presented, followed by discussion. These are similar in nature to those presented to UK trainees in the Final FRCA examination

However, it is the three chapters devoted to management aspects that, for me as an outsider, provided the greatest insight into current differences between anaesthesia in the US and the UK: those on the organization of a preoperative evaluation centre; development of practice guidelines; and preoperative data management. Stephen Fischer describes the Stanford Preoperative Anesthesia Evaluation Center, the effectiveness of which was presented in a special article in *Anesthesiology* (1996; **85**: 196). The centre's first operational goal is 'To improve the patient's, surgeon's, and insurance company's perception of the preoperative evaluation experience'. Gentle coercion sometimes had to be used to persuade surgeons to use the centre: informal guarantees not to cancel a patient; and the assessment appointment must be booked before an operating room is allocated. It appears, inevitably, that most of the assessments, explanations, pain information and patient education are undertaken by individuals other than the one who will actually administer the anaesthetic. Hence, presumably, the urgent need for consensus on preoperative assessment, development of practice guidelines, data collection, and computer feedback programmes to suggest to the assessor possible areas for cost reduction.

In the preface, Dr Sweitzer talks of converging forces that have made this book necessary. Having read the book, it is hard not to conclude that the insurance companies have provided the greatest driving force. In the space of fewer than 30 pages, the word 'cost' appears on no fewer than 22 occasions, usually in association with words such as containment, reduction, control, constraints, and value-added. In the UK, one is starting to detect similar forces at work behind certain NHS initiatives, and I hope that I shall retire before I am no longer 'guaranteed access to the patient'. As anaesthetists, if we are not careful, we will be forced into becoming technicians, merely following a prescription that has been largely determined by someone else. Under such circumstances, where is the doctor-patient relationship and who is medicolegally responsible?

R. A. Mason

Video review: Adult intubation. Volume 3 from Airway Cam Technologies, Inc., PO Box 337, Wayne, PA 19087, USA (www.airwaycam.com). VHS video available in NTSC, PAL and SECAM formats. Duration approximately 28 min. US$149.95

In contrast to flexible fibreoptic intubation, there is a paucity of video teaching material for direct laryngoscopy This has been addressed with a series of videos made using a video camera developed by Dr Levitan of the University of Pennsylvania Medical Center. The video camera lies in the line of sight and records the view as seen by the user.

Volume 3 concerns tracheal intubation of the adult. It deals with anatomy, function, history, laryngoscope design, techniques of laryngoscopy, and tracheal intubation. In the anatomy section, line drawings are accompanied by colour images, and a functional view of anatomy recorded with a flexible fibreoptic rhinolaryngoscope is presented. Vocal cord function is demonstrated clearly in this section by means of a rigid mirrored fibreoptic laryngoscope with a stroboscopic light source. The historical section highlights the techniques developed by Kirstein and Jackson. The latter is particularly welcome, as Jackson's textbook *Bronchoscopy, Esophagoscopy and Gastroscopy. A Manual of Peroral Endoscopy and Laryngeal Surgery* is not widely available. Jackson's emphasis on progressive visualization of landmarks is endorsed. The technique section demonstrates use of the standard Macintosh laryngoscope, as well as the 'Improved Vision' and McCoy variants. My only concern about technique is that insertion of the Macintosh in the midline, rather to the right of the tongue, with subsequent movement into the midline, is advocated. This probably leads to suboptimal tongue control in a couple of cases, although good visualization of the larynx is achieved.

The greatest value of this video is demonstration of the optimum techniques of using straight laryngoscopes. Passage through the paraglossal gutter, the importance of identifying anatomical structures, and optimization of the view, particularly with external laryngeal manipulation, are all demonstrated. Although use of a stylet with a hockey-stick shape can be helpful when the Miller laryngoscope impedes passage of the tracheal tube, many UK anaesthetists will prefer initial passage of a bougie under vision. Use of the Miller, Wisconsin, Philips and Guedel straight laryngoscopes are all discussed and demonstrated.

I have a few minor criticisms. The statement that all fibreoptic laryngoscopes carry green markings is not true of the UK. It is also suggested that the tracheal tube is secured whenever the cuff is passed beneath the vocal cords, but optimal positioning of tracheal tubes is achieved when the black mark above the cuff (almost universal on tracheal tubes) is positioned at the level of the vocal cords. However, these minor points do not detract from the value of this video. It is the best teaching video I have ever seen. Both the technical and clinical material are superb. There is a need for improved training in the use of straight laryngoscopes, and this video complements clinical teaching. Every department should have a copy of this video, and individual anaesthetists who purchase a personal copy will find it a useful aid to improving their technique.

J. Henderson

'Final FRCA' Multiple Choice Questions M.D. Brunner, P.N. Robinson and M. Williams. Published by Butterworth Heinemann, Oxford. Pp. 320; indexed. Price £16.99. ISBN 0-7906-4214-9.

The authors of *Final FRCA: Multiple Choice Questions* laid out these questions according to the syllabus and regulations of The Royal College of Anaesthetists' final fellowship examination. The aim of the authors is to test factual knowledge and, at the same time, to educate the reader.

In the introduction of the book, the authors describe the MCQ examination and advise as follows: read the questions carefully; do not guess; answer as many MCQs as you can; and aim to pass the MCQ examination with a score of 2. The book consists of five examination papers each having 90 multiple choice questions. The length of each MCQ paper mirrors the real examination paper; it is therefore suggested that it may help to time oneself by, in effect, doing a mock-examination. But these MCQs are not original questions from the final FRCA examination.

The question stems are of variable length. The simple stems are used to test simple facts. For instance, the question about the causes of hypercalcaemia presents five answers–thiazide diuretics, lithium, aminophylline, Conn's Syndrome and phaeochromocytoma (p. 184). The complicated stems help to assess a reader's ability to deduce facts from basic core knowledge; for example, a question about physiological effects of α_2 agonists includes the false statement that respiration is not affected and Pa_{CO_2} is not changed (p. 168). In fact, Pa_{CO_2} will be slightly raised.

The MCQs cover the key areas of medicine and surgery, applied basic sciences, clinical management, intensive therapy, and anaesthesia and pain management. There is a similar number of MCQs in each area as in the FRCA examination paper. There are 20 questions in medicine and surgery, 20 in applied basic sciences, 10 about clinical management, 20 in intensive therapy and 20 in anaesthesia and pain management in each paper. The questions within each paper are well balanced. But some of the topics, such as renal failure, clotting systems, nitric oxide, anaphylaxis and adverse reactions, hypothermia, and gas analysis and cylinders, appear up to six times through the book.

I very much appreciated the answers being placed on the opposite page to the questions. It saves time, as it stops the reader going backward and forward over the pages and therefore facilitates self-testing. It also keeps one at the exercise! The answers are well structured, concise and constructive, particularly about disseminated intravascular coagulopathy (p. 75) and ulcerative colitis (p. 107).

It is disappointing that the book does not have any references in the answer text, either on the same page or at the end of the book. I had to check the validity of the answers from sources such as the MEDLINE database; *Anesthesia* (4th Edition, 1994, Miller RD ed.); *Principles and Practice of Anesthesiology* (2nd Edition, 1998, Longnecker DE, Tinker JH and Morgan GE Junior); *Oxford Textbook of Critical Care* (1999, Webb AR, Shapiro MJ, Singer M and Suter PM).

There are some interesting, albeit somewhat esoteric questions in the book. For instance, in the question about fat embolus, it was interesting to find out that intramedullary pressure may rise up to 1400 mm Hg during surgery on the femur (p. 45). In one of the questions about anaphylaxis, I learned that tryptase samples could even be taken post-mortem for diagnostic purposes (p. 117). I encountered a few errors in the answers to questions about the boiling point of carbon dioxide (p. 29), and the management of myxoedema coma (p. 173).

Finally, the authors demonstrated that there is more to life than examinations! It was worth persisting to the 91st question of the fifth paper in the book, if only for amusement, despite the fact that, as a post-fellowship trainee from Liverpool, I am not an Arsenal Football Club supporter!

In summary, this is a well-structured, balanced and indexed MCQ book with a good layout and content. It is only unfortunate that it does not offer any references.

G Sidaras

Guide to Contributors

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Dr J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005. E-mail: bja@liv.ac.uk

Papers

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publisher.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki and should normally include a statement of approval from an appropriate Ethics Committee. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted. Studies from the UK should specify the Home Office Licence number; from elsewhere, a statement of approval from an appropriate licensing authority.

Legal considerations

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the authors and publishers.

Preparation of manuscript

Four copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss. Where possible, manuscripts should also be submitted on disk. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the three other sets may be photocopies.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all the authors. There should be a clear declaration of any financial or commercial interest which any author may have in the material. The Editor may wish to see raw data if necessary.

Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:-

Title page
Summary, including Keywords
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Illustrations

Title page

There should be a separate title page, including the name(s) and address(es) of all author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given and referenced at the appropriate place in the author list by superscript numbers. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spacing should be included.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, methods, results and conclusions, and normally should

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be of 50–150 words. It may be used as it stands by abstracting journals.

Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the international non-proprietary name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of results, while concise, should permit repetition of the investigation by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability.

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially. Individuals named must be given the opportunity to read the paper and approve their inclusion in the acknowledgements, before the paper is submitted.

References

There should be a list of references at the conclusion of the paper, commencing on a new sheet.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically.

References in text, tables and legend should be identified by arabic numbers appearing in the text in superscript, for example ^{5} or $^{5-7}$ or ^{5}<space>^{16} for unrelated references. When a table, figure is first mentioned, its reference must continue the sequence.

Use the style of references adopted by the US National Library of Medicine and used in *Index Medicus*. The titles of journals should be abbreviated.

The names and initials of more than six authors should be abbreviated to three authors followed by *et al.*

Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase 'in press' replacing volume and page number. Information from manuscripts submitted but not yet accepted should be cited in the test as unpublished observations.

Examples of correct forms of references:

Journals:

1. Brown BR jr, Gandolphi AJ. Adverse effects of volatile anaesthetics *Br J Anaesth* 1987; **59**: 14–23

Chapter in a book:

2 Hull CJ Opioid infusions for the management of postoperative pain. In: Smith G, Covino BG, eds. *Acute Pain.* London: Butterworths, 1985; 155–79

Monographs:

3 Moore, DC. *Regional Block*, 4th Edn. Springfield, Illinois Charles C. Thomas, 1979

Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* journals.

It is essential that authors verify the content and detail of references which they list against the original articles, as this responsibility cannot be accepted by either Editors or publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with Arabic numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used. Footnotes are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black indict ink on white paper and, if in sets, should be presented at a uniform magnification. Illustrations should be clearly

numbered on the back, preferably in soft pencil, with reference to the text, and using Arabic numbers. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the figure (and not in the legend) should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ × +

The names of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It should be noted that A4-size figures generated by computer are usually unacceptable (see Extended Guide to Contributors—*Br J Anaesth* 2000; **84**: 131–7).

General information

Instructions to the printer. Words to be printed in lowercase italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Three possible grades are available, and may be indicated by the following letters of identification.

A **Results (bold)**
B *Lung function studies* (italics, ranged left)
C *Volume.* Large volumes . . . (italics, ranged left, text run on)

Symbols and abbreviations. In accordance with Editorial adoption of SI units, abbreviations and symbols should follow the conventions described in the booklet *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors* (D. N. Baron, ed.) (1988), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with 'z' rather than 's' spelling in, e.g. organize, organization.

Short communications

Authors are encouraged to submit short manuscripts suitable for rapid publication. In general, these should conform to the requirements outlined above, but with the following differences:

Format. Summary; Introduction (not headed); Methods and results; Comment.

Size. Not more than 6 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words).

Correspondence

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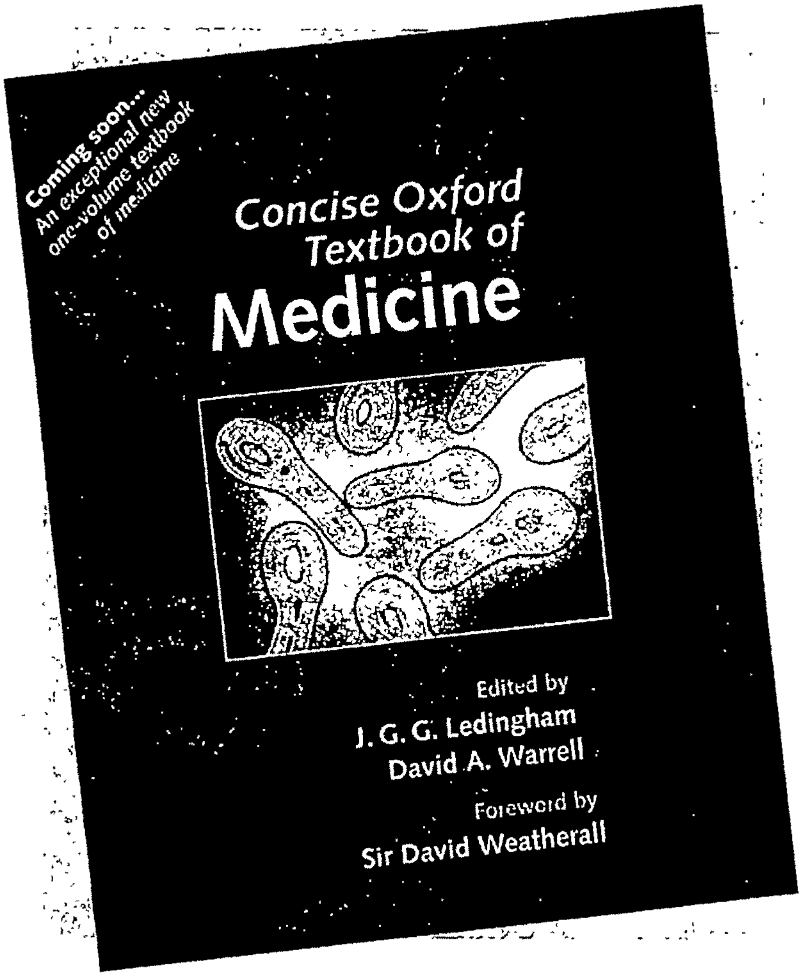

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